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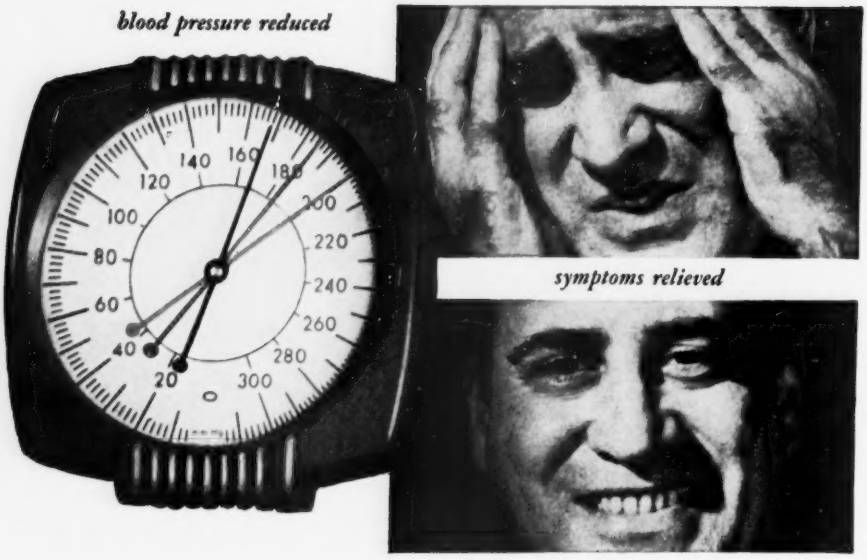

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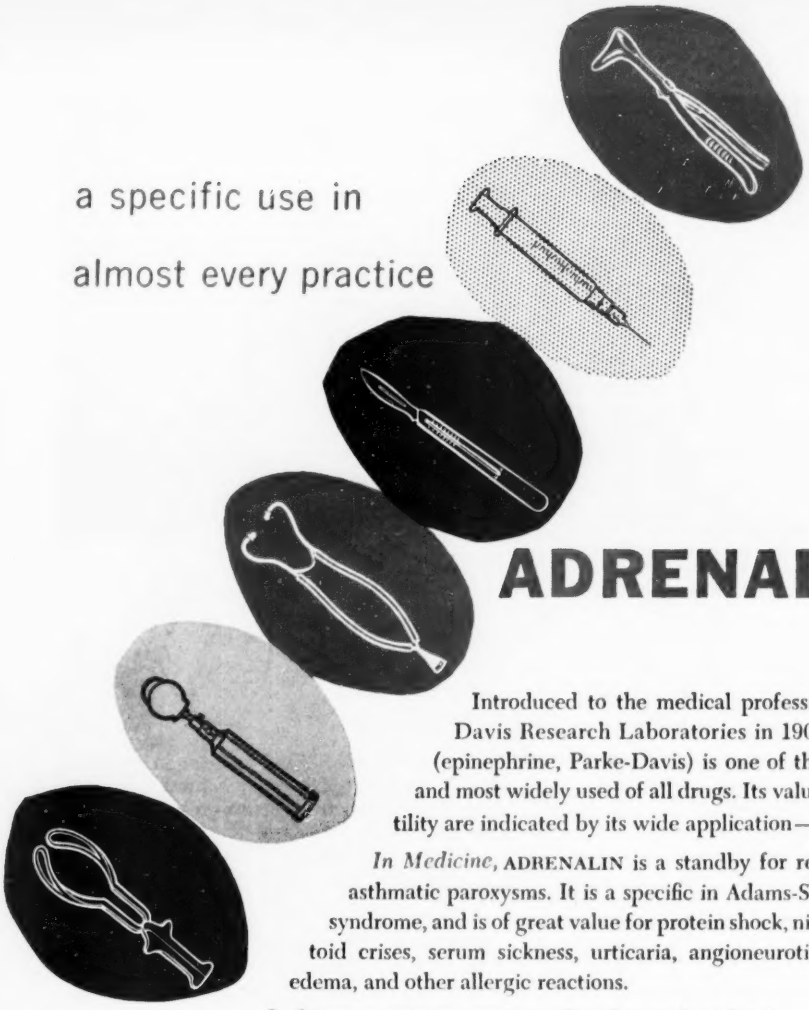

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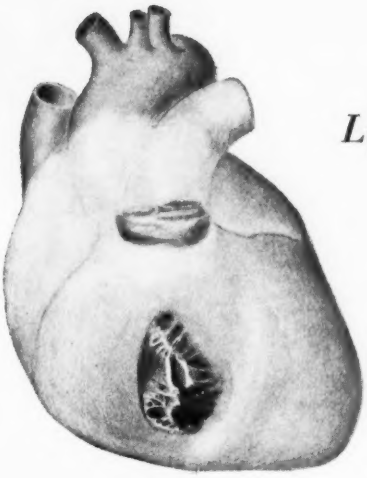

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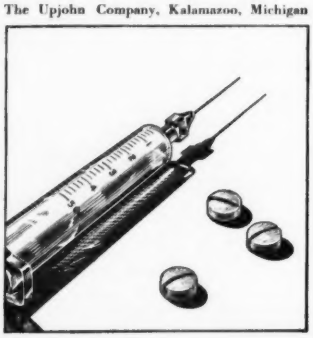

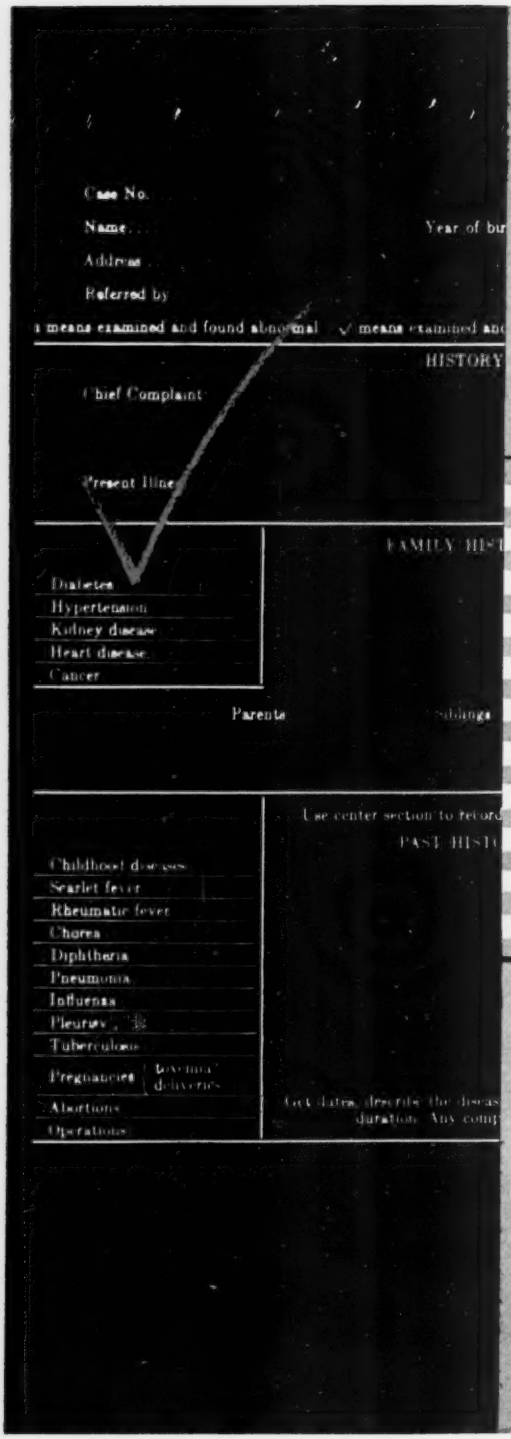

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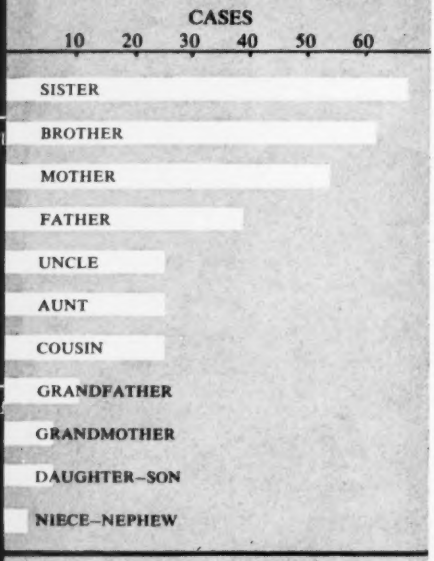

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ARCHIVES OF INTERNAL MEDICINE

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Editorials

DR. RUSSELL M. WILDER RETIRES FROM A. M. A. ARCHIVES OF INTERNAL MEDICINE EDITORIAL BOARD

IT IS WITH considerable regret that the retirement of Dr. Russell M. Wilder from the ARCHIVES Editorial Board after twenty-one years of continuous service is announced. He has served enthusiastically and well in that capacity, while shouldering a multitude of other responsibilities which have made him a widely known and respected figure in American medicine. After his early training at the University of Chicago and Rush Medical College he was a member of the Mayo Clinic from 1919 to 1929. He then accepted the post of chairman of the department of medicine in the University of Chicago from 1929 to 1931, returning then to Rochester, Minn., where he served as head of the department of medicine of the Mayo Foundation until 1950. At this time he became director of the National Institute of Arthritis and Metabolic Diseases of the United States Public Health Service, a post which he relinquished to retire to his home in Rochester. During these years, in addition to acting as chairman and member of the Food and Nutrition Board of the National Research Council throughout World War II and beyond, he found time to write two books on diabetes, be co-author of several others, contribute upward of 200 articles to the medical literature, and to participate in the activities of a host of distinguished medical societies. As his associates of many years regretfully bid him adieu from the ARCHIVES, they rejoice that his capacities for enjoyment of life among his colleagues and neighbors of a long and useful medical career remain unimpaired.

NEW MEMBERS OF THE ARCHIVES EDITORIAL BOARD

IT IS WITH great satisfaction that two new members are welcomed to the ARCHIVES Board to fill the vacancies created by Dr. Wilder's retirement and the untimely death of Dr. Reginald Fitz.

DR. WILLIAM BENNETT BEAN

Dr. William Bennett Bean is already a familiar figure to ARCHIVES readers through many noteworthy contributions, the most recent of which was his delightful essay, "Caritas Medici," in the July issue. He has the gift of elegant and succinct expression, and the slant of his medical thinking can best be set down in his own words, quoted from a recent letter, "My medical interests are eclectic and universal. In addition to cardiology, nutrition and liver disease, my favorite hobby is deflating the stuffed shirts."

Dr. Bean has been professor and head of the department of Internal Medicine of the State University of Iowa College of Medicine since 1948. After his graduation from the University of Virginia Department of Medicine he interned at Johns Hopkins Hospital and began a long career of training and teaching which included posts at Boston City Hospital, Thorndike Memorial Laboratory, Harvard University, and University of Cincinnati College of Medicine. After ten years in the latter institution, at which time he had attained the rank of Associate Professor of Medicine, he moved on to his present post in Iowa. During World War II he was director of the Armored Medical Research Laboratory at Fort Knox, Ky.

In addition to accomplishing many fundamental pieces of research he has served on the editorial boards of the *Cincinnati Journal of Medicine, Nutrition Reviews, Journal of Clinical Investigation,* and *Journal of Laboratory and Clinical Medicine.* He was editor of a volume of medical monographs in 1951. The A. M. A. ARCHIVES OF INTERNAL MEDICINE is happy to welcome him to its editorial board.

DR. CHARLES S. DAVIDSON

It seems peculiarly appropriate that Dr. Davidson should become a member of the ARCHIVES Editorial Board at this time because his research interests have so closely paralleled those of Dr. Wilder, under whom he served as chief of clinical research in the National Institute of Arthritis and Metabolic Diseases of the United States Public Health Service. He has also been an associate of Dr. Fitz in Harvard Medical School.

After receiving his M.D. at McGill in 1939 he interned in San Francisco Hospital, then entered Thorndike Memorial Laboratory, in Boston, where he has remained in active research except for the year 1951-1952, spent in Bethesda, Md. During this entire period he has been a physician of the Boston City Hospital, becoming associate director of the Second and Fourth Medical Services in 1948. Starting as an assistant in medicine in Harvard Medical School in 1942, he has now attained the rank of associate professor in that institution. His investigative work has included fundamental studies on blood coagulation, especially in hemophilia; the nature of a proteolytic enzyme derived from blood plasma; protein metabolism in persons with extensive burns; the mechanism of action of vitamin K_1 oxide; the role of protein in human nutrition; treatment of chronic liver disease; the metabolism of human serum albumin administered to men; studies in scurvy, and many other allied subjects.

This extensive background of research in metabolic disorders, together with constant contact with patients, should make him eminently well prepared for the editorial duties he is now undertaking.

RUSSELL M. WILDER, M.D.

WILLIAM B. BEAN, M.D.

CHARLES S. DAVIDSON, M.D.

MERCURIAL DIURESIS

DURING the past fifteen to twenty years, studies of the pathogenesis of congestive heart failure have been directed primarily at the mechanisms responsible for the impaired renal excretion and/or retention of extracellular electrolytes and water. As a result, most advances in therapy have been concerned with the prevention of fluid accumulation and the facilitation of removal of excessive fluid. Since the organic mercurial diuretics provide the most rapid and efficient means of removing salt and water, their use has increased considerably. The availability of subcutaneously administerable preparations [1] whose ease of administration and predictability of action have led to the advocacy of self administration in selected patients [2] has contributed further to the growing use of these agents. The promise of oral mercurial diuretics, as yet unfulfilled, may lead to still greater usage.

Certain properties common to the presently used mercurials contribute to their inherent safety. Intravenous administration is now rarely, if ever, necessary, so that acute cardiotoxic effects are no longer encountered. Secondly, the degree of diuresis resulting from any single injection appears to be fairly proportional to the amount of fluid previously retained,[3] provided it has not been trapped in body cavities less accessible to the effects of the mercurial. As the edema recedes and the patient approaches his "dry" weight, the electrolyte loss and urine volume per injection decrease. Therefore, before electrolyte depletion can have exerted any irreversible, harmful effects, the patient will have ceased to respond to the drug. Consequently, the simple measurement of weight loss or urinary volume during the twenty-four hours following an injection is sufficient to ascertain its efficacy and prevent those harmful effects attributable to too frequent administration of these compounds.

Clinical studies and empiricism have combined to increase our understanding of certain aspects of mercurial action. Despite some earlier doubts, it is well established that the diuretic activity of these drugs is confined to the kidney.[4] Dosage response

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curves have been established.[5] Since those mercurials lacking a xanthine component produce no significant changes in glomerular filtration, the marked enhancement of electrolyte and water excretion must reflect a specific inhibition of renal tubular reabsorption. Reversible impairment of other renal tubular functions has been demonstrated. Thus, uric acid[8] and glucose[6] reabsorption are diminished, the tubular secretion of *p*-aminohippurate is decreased,[7] and tubular transport of potassium in both directions is reduced.[8]

Augmentation of mercurial diuresis by each of several regimens has been well documented. The enhancement of diuresis by acid salts (and, conversely, its reduction following alkaline salts) appears to be independent of the specific anions involved.[9] The intravenous administration of aminophylline during maximal mercurial activity frequently results in a significantly increased diuresis.[10] Since aminophylline produces both an increase in renal hemodynamics and a decrease in tubular reabsorption of salt and water,[11] as well as secondary effects on other circulatory functions, it is difficult to assess accurately the relative effect of each action. However, since, first, the elevation of glomerular filtration is transient; second, the enhancement of diuresis occurs even with slight rises in glomerular filtration, and, third, small changes in tubular activity produce much greater effects on electrolyte excretion, it is probable that the synergistic action of aminophylline is dependent largely on its tubular action. The efficacy of mercurial diuresis may be increased also by recumbency,[12] which results in increased cardiac output and renal circulation, diminished tubular reabsorption of electrolytes and water,[13] and possibly reduced production of antidiuretic hormone,[14] all of which would tend to aid the mercurial's action.

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The work of Burch and his colleagues,[15] employing radiomercury, has shed considerable light on the distribution and excretion of the injected mercury. After the administration of the usual dose of a diuretic (80 mg. of mercury), most of the mercury is found in the kidneys, and it is virtually entirely excreted in the urine within twenty-four to thirty-six hours. A small quantity is rapidly taken up by the liver, less than 5% of the injected dose being excreted via the bile and feces.

In vitro studies have revealed an inhibitory effect of some mercurials on specific renal enzyme systems.[16] The very rapid reversal of mercurial activity by dimercaprol (BAL) and other sulfhydryl compounds [17] is very suggestive of a bond between the mercury and sulfhydryl groups of the enzymes involved, but the clinical implications of cellular activity have not been explored.

The unresponsiveness of certain patients to mercurial diuretics has recently received deserved attention. According to Weston and his colleagues,[18] while a number of mechanisms may be responsible for counteracting the effects of the mercurial, the impaired tubular load of electrolyte may be most important, since increasing the amount of salt and water filtered, either by aminophylline or the infusion of hypertonic saline, results in increased diuresis. However, it should be realized that the role of tubular load is not a simple one, since the relative influences of the two factors which determine it, namely, plasma concentration and filtration rate, may be highly unequal.

Notwithstanding the widespread use of mercurials, many aspects of the mechanisms underlying their activity are as yet unknown. This is, in large part, due to the fact that the fundamental tubular cellular mechanisms involved in electrolyte excretion have yet to be elucidated.

First, even the site of action of these agents has been a source of some controversy, with little conclusive evidence as yet available. Thus, Duggan and Pitts,[19] on the basis of the fact that mercurials, in maximal doses, depressed only the small fraction of renal tubular sodium reabsorption ascribed to the distal tubules, inferred that the action of these agents was exerted on the distal segment although a partial effect on the proximal tubules was not excluded. Brodsky and Graubarth,[20] on the other hand, employing hydropenic dogs, found that the increased urinary volume, as in osmotic diuresis, paralleled the number of osmotically active particles claiming excretion, from which they concluded that mercurials acted primarily on the proxi-

15. Milnor, P.; Burch, G.; Ray, T.; Threefoot, S., and Berenson, G.: Considerations of Renal, Hepatic, and Extremital Arteriovenous Differences in Concentration of Radiomercury of a Mercurial Diuretic, J. Clin. Invest. **29**:72, 1950.

16. Handley, C. A., and Lavik, P. S.: Inhibition of the Kidney Succinic Dehydrogenase System by Mercurial Diuretics, J. Pharmacol. & Exper. Therap. **100**:115, 1950.

17. Handley, C. A., and LaForge, M.: Effect of Thiols on Mercurial Diuresis, Proc. Soc. Exper. Biol. & Med. **65**:74, 1947. Farah, A., and Maresh, G.: Influence of Sulfhydryl Compounds on Diuresis and Renal and Cardiac Circulatory Changes Caused by Mersalyl, J. Pharmacol. & Exper. Therap. **92**:73, 1948.

18. Weston, R. E.; Escher, D. J. W.; Grossman, J., and Leiter, L.: Mechanism Contributing to Unresponsiveness to Mercurial Diuretics in Congestive Failure, J. Clin. Invest. **31**:901, 1952.

19. Duggan, J. J., and Pitts, R. F.: Studies on Diuretics: I. The Site of Action of Mercurial Diuretics, J. Clin. Invest. **29**:365, 1950.

20. Brodsky, W. A., and Graubarth, H. N.: Mechanism of Mercurial Diuresis in Hydropenic Dogs, Am. J. Physiol. **172**:67, 1953.

mal tubules, the impaired reabsorption resulting in the passage of much larger quantities of electrolytes and water than could be handled by the distal segment. Somewhat similar conclusions were drawn by Farah[21] and Weston,[22] although effects on the distal tubule were not excluded. Interestingly enough, the production of ammonia and titratable acid, two commonly accepted distal tubular functions, are not depressed by mercurials.[23]

Secondly, little is known of the mechanisms whereby acid salts exert their synergistic effects. Neither the pH of the plasma nor its chloride concentration appears to be the determining factor. Hilton[24] has demonstrated that ammonium chloride produces increased mercurial diuresis in normal subjects even after their acidosis is compensated with return of plasma pH and bicarbonate concentration to normal. Few definitive data are available on the intracellular ionic concentrations and their influence on tubular transport.

Thirdly, despite a number of allusions in the literature to the role of ionized as distinct from unionized mercury,[25] information has not accumulated on that form of mercury which, at a cellular level, is responsible for the reversible depression of tubular function. This point is of some interest because of the literally anachronistic action of mercury in the kidney. Immediately following injection, mercury is taken up by the kidney, held for a short time, then slowly released.[26] Nevertheless, much of an injected dose of mercury appears in the urine prior to the onset of diuresis.[27] What takes place within the tubule cells during this latent period is entirely unknown. Conversely, the diuresis is observed to subside two to four hours after intravenous injection, or at a time when a considerable fraction of the injected dose is still in the body and in the process of being excreted. Apparently, at this time the kidney is relatively refractory to the mercury passing through it.

This observation impinges upon an important, though as yet poorly understood, aspect of mercurial action, namely, the factors responsible for cessation of diuresis. It has been observed that many of the mercurials in common use appear to have approximately equal pharmacologic effects on electrolyte excretion. This, possibly, may be due to the fact that an approximately equal fraction of the total mercury is converted to an active form. Considering, however, that these compounds differ widely in their chemical configuration, this explanation does not appear to be tenable. As an alternative hypothesis, it is quite possible that following diuresis the

21. Farah, A.; Cobbey, T. S., and Mook, W.: Concentration Changes in Urinary Electrolytes Produced by Mercurial Diuretics, Proc. Soc. Exper. Biol. & Med. **81**:601, 1952.

22. Weston, R. E.; Grossman, J.; Borun, E. R., and Leiter, L.: Effect of Mercurial Diuretics During Pitressin Antidiuresis in Man, Fed. Proc. **11**:171, 1952.

23. Weston, R. E.; Grossman, J., and Leiter, L.: The Effect of Mercurial Diuretics on Renal Ammonia and Titratable Acidity Production in Acidotic Human Subjects with Reference to Site of Diuretic Action, J. Clin. Invest. **30**:1262, 1951.

24. Hilton, J. G.: Potentiation of Diuretic Action of Mercuhydrin by Ammonium Chloride, J. Clin. Invest. **30**:1105, 1951.

25. Sollmann, T.; Schreiber, N. E.; Cole, H. N.; Gammiel, J. A., and Rauschholt, J. E.: The Diuretic Effects of Various Mercurial Treatments, Am. J. Physiol. **93**:689, 1930.

26. Weston, R. E.; Grossman, J.; Lehman, R. A.; Ullmann, T. D.; Halperin, J. P., and Leiter, L.: Renal Extraction and Excretion of Mercury in Man Following Intravenously Administered Mercurial Diuretics, J. Clin. Invest. **30**:1221, 1951.

27. Grossman, J.; Weston, R. E.; Lehman, R. A.; Halperin, J. P.; Ullmann, T. D., and Leiter, L.: Urinary and Fecal Excretion of Mercury in Man Following Administration of Mercurial Diuretics, J. Clin. Invest. **30**:1208, 1951.

rapid loss of electrolytes and fluid calls into play a number of mechanisms which counteract and overcome the action of the mercurial. A discharge of salt-retaining adrenal cortical hormone (s) may provide one possible explanation. Thus, the completion of mercurial diuresis may be due not to simple subsidence of the drug's action, but may be the result of actively induced bodily countermeasures. This problem requires considerable further study and analysis.

During the past three to four years, the mercurial diuretics have been implicated in the causation of the low salt syndrome.[28] While overly frequent administration may conceivably produce some depletion and low electrolyte concentrations, there is ample reason to believe that other factors may play a more prominent part in the pathogenesis of this state. The growing use of sodium-restricted diets may be partly responsible in that loss of sodium is not easily replenished. Ammonium chloride administration and other therapeutic regimens result in potassium depletion[29]; such loss of cellular potassium may be accompanied by the migration of water from cells with dilution of the extracellular fluid until there is reestablishment of osmotic equilibrium. Evidence has recently accumulated[30] that water retention, rather than, or in addition to, simple depletion may be most responsible for the dilution of plasma electrolytes in hyponatremic states. Such cardiac patients who, for various reasons (infection, digitalis escape, or toxicity), suffer intensification of their congestive failure frequently exhibit rapid dilution—without loss—of their extracellular electrolytes, a process which may be readily reversed by adequate therapy of the underlying etiology, but which is not benefited by the administration of hypertonic saline solutions. While, then, the injudicious use of mercurial diuretics may produce some electrolyte depletion, other factors, producing primary water retention, hence dilution, in severely ill cardiac patients usually predominate.

From the preceding review, it is apparent that despite the unquestioned value of the mercurial diuretics, many subtler aspects of their pharmacologic activity on a cellular level still require detailed study.

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28. Schroeder, H. A.: Renal Failure Associated with Low Extracellular Sodium Chloride: Low Salt Syndrome, J. A. M. A. **141**:117, 1949.

29. Grossman, J.; Weston, R. E.; Hanenson, I. B.; Borun, E. R.; Guerin, H. A.; Ullmann, T. D., Wolfman, M., and Leiter, L.: Metabolic Studies on Ammonium Chloride Acidosis in Patients in Congestive Heart Failure, Fed. Proc. **12**:57, 1953.

30. Weston, R. E.; Borun, E. R.; Grossman, J.; Guerin, H. A.; Ullmann, T. D.; Wolfman, M., and Leiter, L.: Acute Hyponatremia Due to Water Retention in Congestive Heart Failure, Proceedings 25th Scientific Sessions of American Heart Association, Cleveland, April 17-20, 1952, p. 13.

TREATMENT OF STAPHYLOCOCCIC INFECTIONS WITH ERYTHROMYCIN

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AND
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FROM THE standpoint of antibiotic therapy, infections caused by staphylococci constitute one of the major problems at the present time. In hospitalized patients approximately 70% of staphylococcic infections are caused by penicillin-resistant organisms and 40 to 60% are resistant to chlortetracycline (aureomycin) and oxytetracycline.[1] In many instances, the only antibiotics available for treatment are bacitracin and chloramphenicol, both of which must be administered with caution because of possible toxic reactions.

In vitro studies indicate that a new antibiotic, erythromycin, should be a highly effective agent for the therapy of staphylococcic infections. To date, only isolated case reports have appeared.[2] During the past several months we have had the opportunity of observing the effects of erythromycin therapy in 34 patients with infections caused by antibiotic-resistant staphylococci. Results of treatment were uniformly good and will be described in the present report.

PLAN OF STUDY

Selection of Patients.—Thirty-four patients with staphylococcic infections were treated with erythromycin from December 1952 through June 1953. With one exception, the patients were all adults, and all were hospitalized on the medical or surgical wards of the King County Hospital while under therapy. Twenty-two patients were suffering from soft tissue infections, 10 had osteomyelitis, and 2 had conditions listed as miscellaneous infections.

Bacteriological Studies.—In most instances staphylococci were isolated from the infected areas in pure culture. Close contact was maintained with the routine bacteriological laboratory, and growth of a pure culture of Staph. aureus led to recognition and prompt institution of therapy in a number of patients in various parts of the hospital.

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1. Finland, M., and Haight, T. H.: Antibiotic Resistance of Pathogenic Staphylococci: Study of 500 Strains Isolated at Boston City Hospital from October, 1951, to February, 1952, A. M. A., Arch. Int. Med. **91**:143, 1953. Needham, G. M., and Nichols, D. R.: Recent Changes in Sensitivity of Micrococcus Pyogenes to Various Antibiotic Agents, J. Lab. & Clin. Med. **41**:150, 1953. Kirby, W. M. M., and Ahern, J. J.: Changing Pattern of Resistance of Staphylococci to Antibiotics, to be published.

2. (*a*) Haight, T. H., and Finland, M.: Laboratory and Clinical Studies on Erythromycin, New England J. Med. **247**:227, 1952. (*b*) Heilman, F. R.; Herrell, W. E.; Wellman, W. E., and Geraci, J. E.: Some Laboratory and Clinical Observations on a New Antibiotic, Erythromycin (Ilotycin), Proc. Staff Meet., Mayo Clin. **27**:285, 1952. (*c*) Smith, J. W.; Dyke, R. W., and Griffith, R. S.: Absorption Following Oral Administration of Erythromycin, J. A. M. A. **151**:805, 1953.

Both the tube-dilution and disc methods of performing sensitivity tests were employed. With the tube method, organisms were regarded as sensitive when they were inhibited by 5 γ per milliliter or less of chlortetracycline and oxytetracycline, 10 γ or less of chloramphenicol, 5 units or less of penicillin and bacitracin, and 2 γ per milliliter or less of erythromycin. With the disc method, a single disc (Bacto-Sensitivity Disks, Difco) was used for each antibiotic as follows: penicillin 10 units; chlortetracycline, oxytetracycline, and chloramphenicol 60 γ each, and erythromycin 10 γ. Staphylococci were regarded as sensitive when there was a total diameter (disc plus clear zone of inhibition) of 15 mm. or more with chlortetracycline and oxytetracycline discs, 17 mm. or more with penicillin, and 20 mm. or more with chloramphenicol and erythromycin.

All 34 of the strains of Staph. aureus were resistant to penicillin, chlortetracycline, and oxytetracycline. Infections caused by organisms sensitive to these antibiotics occurred in the hospital throughout the period of this study, but in those instances the patients were treated with antibiotics other than erythromycin. Results of a typical sensitivity test are presented in

TABLE 1.—*Results of a Typical Antibiotic Sensitivity Test* *

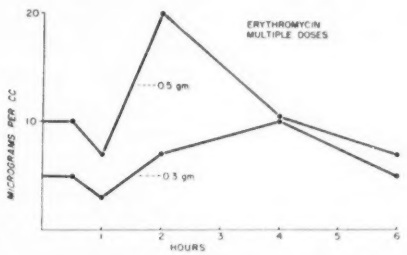
Tube Method †						Disc Method ‡				
A	O	C	P	E	B	A	O	C	P	E
>50	>50	5	>50	<0.5	<1	6	6	30	11	24

A = chlortetracycline (aureomycin); O = oxytetracycline; C = chloramphenicol; P = penicillin; E = erythromycin; B = bacitracin.

* All the 34 strains of Staph. aureus were resistant to penicillin, chlortetracycline, and oxytetracycline and were highly sensitive to erythromycin. Note the close correlation between results of the tube-dilution and disc methods.

† Concentration in units or micrograms per milliliter causing complete inhibition of growth.

‡ Diameter of zone of inhibition in millimeters, including 6 mm. disc.



Representative serum concentrations of erythromycin in patients receiving 0.3 or 0.5 gm. of the antibiotic in acid-resistant tablets every six hours.

Table 1. In general, there was an excellent correlation between results of the tube-dilution and disc methods of performing the sensitivity tests. This is a reflection of the fact that the organisms tended to be either highly resistant or highly sensitive to the various antibiotics. All the 34 strains were sensitive to bacitracin and erythromycin, and only 3 were resistant to chloramphenicol. Erythromycin serum concentrations were performed according to a technique which has been described elsewhere.[3]

Therapeutic Regimen.—Erythromycin [4] was administered in tablet form in doses of 0.3 or 0.5 gm. every six hours. The tablets were administered with a full glass of water and were given at 3:00 a. m., 9:00 a. m., 3:00 p. m., and 9:00 p. m., so that food would not interfere with absorption. Therapy was continued for 7 to 14 days in most instances, but in a few cases it was administered for as long as two months.

3. Kirby, W. M. M.; Maple, F. M., and O'Leary, B.: Erythromycin Serum Concentrations Following Administration in Acid-Resistant Tablets, Antibiotics & Chemother. **3**:473, 1953.

4. Erythromycin was supplied by Eli Lilly & Company.

TABLE 2.—*Summary of Data on Patients with Staphylococcic Infections Treated with Erythromycin*

Patient	Age, Yr.	Clinical Problem	Other Therapy	Result
Soft Tissue Infections				
1	75	Wound breakdown with large abscess in deeper tissues 10 days after open reduction of right hip fracture	Wound opened, drains inserted	Improved initially; wound became secondarily infected with E. coli, and patient died later of pulmonary infarct
2	43	Radical neck dissection for metastatic cancer, followed by deep wound infection and spiking fever; poor response to 10-day course of oxytetracycline	Open drainage of wound	Excellent response, with rapid closure of wound
3	68	Extensive wound infection right thigh following open reduction of fracture right femur with tibial bone graft; no response to 10 days of penicillin and oxytetracycline; organism resistant to these antibiotics	Repeated needle aspiration of pus; wound not opened widely	Immediate subjective response, with increase in appetite and decline of fever; 2 gm. daily of erythromycin for 2 months, with eventual eradication of infection
4	31	Infected abdominal wound following hysterectomy	Wound partially opened	Prompt healing of wound
5	46	Decubitus ulcer, poor response to chlortetracycline	Full thickness skin flap	Infection controlled, graft successful
6	47	Aplastic anemia, abscesses over buttocks	Abscesses opened and drained	Temporary improvement, later relapse
7	40	Infected cutdown on leg with fever and marked local swelling and redness	None	Striking response, prompt healing
8	37	Infected scalp wound following removal of bone flap	None	Prompt cure
9	27	Infected abdominal wound following hysterectomy	Wound opened and drained	Prompt cure
10	36	Decubitus ulcers right thigh from hip spica cast	None	Prompt cure
11	38	Decubitus ulcer right buttock	Debridément	Gradual improvement, later covered with graft
12	50	Stasis ulcer and abscess over left tibia	None	Cure
13	45	Acute epididymitis, no improvement with chlortetracycline	Surgical drainage	Excellent response
14	37	Wound infection following ventral hernia repair	Wound partially opened	Prompt cure
15	50	Abscess formation and wound breakdown following amputation right lower leg	Wound opened widely	Infection subsided promptly, wound closed
16	60	Infection of wound and subcutaneous tissues following open reduction of intertrochanteric fracture of right leg	Needle aspiration of pus	Afebrile in 3 days, infection subsided completely
17	65	Compound fracture of tibia, with wound breakdown following closure	Wound opened and drained	Marked improvement within 3 days, eventual healing
18	53	Wound infection following sympathectomy	Pus drained by partially opening wound	Prompt cure
19	66	Arteriosclerotic gangrene of foot with ulceration and cellulitis	None	Cellulitis and infection subsided, foot then amputated,
20	23	Cellulitis and abscess of buttock in a debilitated patient	None	Some improvement, but drainage persisted
21	68	Left hip prosthesis, with recurrence of cellulitis and drainage	None	Cellulitis subsided promptly and drainage stopped, but later recurred
22	79	Infected wound at site of insertion of Smith-Petersen nail	None	Cellulitis subsided, small sinus tract remained
Osteomyelitis				
23	18	Osteomyelitis of spine of right scapula multiple draining sinuses, and staphylococcic empyema following gunshot wound	Removal of infected bone; drainage and decortication of empyema	Gradual improvement, complete recovery
24	45	Chronic osteomyelitis lumbar spine; 2 episodes of fever, cellulitis, and increased drainage were treated with erythromycin	None	Both flareups were promptly controlled by erythromycin; organisms eventually became highly resistant to erythromycin
25	74	Chronic osteomyelitis right femur	Saucerization of bone	Excellent healing of wound; apparent cure
26	69	Chronic osteomyelitis right wrist	Infected carpals removed	Wound healed without complications
27	72	Chronic osteomyelitis following amputation of right leg above the knee	Amputation higher up, with primary closure	Uneventful healing of wound

TABLE 2.—*Summary of Data on Patients with Staphylococcic Infections Treated with Erythrombycin*—Continued

Patient	Age, Yr.	Clinical Problem	Other Therapy	Result
28	46	Chronic osteomyelitis right tibia; bone graft, with infection and breakdown of wound; little if any response to chloramphenicol	Debridément	Wound became clean, and osteomyelitis was arrested with erythromycin therapy
29	48	Chronic osteomyelitis right femur	Sequestrectomy	No improvement noted with erythromycin therapy
30	75	Diabetic gangrene right foot with osteomyelitis of great toe; poor response to penicillin and chlortetracycline postoperatively	Amputation right great toe and head of metatarsal	Wound healed with erythromycin
31	62	Draining area over left humerus for 3 years, with little bone involvement	Sinus tract removed	Excellent healing of wound
32	2	Osteomyelitis third metatarsal right foot	Sequestrectomy	Wound healed uneventfully with erythromycin
Miscellaneous Infections				
33	68	Pneumococcic pneumonia with bacteremia; secondary staphylococcic pneumonia appeared after 5 days of therapy with penicillin and chlortetracycline	None	Improved temporarily with erythromycin; sputum was overgrown with Proteus vulgaris, and therapy was changed to chloramphenicol; died after 12 days, with multiple staphylococcic abscesses of internal organs
34	54	Peritonitis and staphylococcic abscess in right lower quadrant following gastric resection	Open drainage	Moderate initial improvement with erythromycin; peritoneal cultures became overgrown with Proteus vulgaris, which was also cultured from the blood stream; chloramphenicol was administered, and after a stormy course there was eventually a complete recovery

RESULTS

Toxicity.—Virtually no side reactions to erythromycin were encountered. The tablets were surprisingly well tolerated even by the sickest patients. Nausea and vomiting occurred in three cases but in all instances appeared to be related more to the underlying disease than to the medication. Most patients noted that the stools tended to become odorless, and some felt less constipated than usual under hospital conditions. However, diarrhea did not occur in a single instance. Three patients received 2 gm. of erythromycin daily for two months without noting any untoward effects.

Serum Concentrations of Erythromycin.—For a number of the patients blood was drawn at appropriate intervals and serum concentrations of erythromycin were determined. There was considerable variability, but in general the levels were remarkably high and well sustained. When 0.5 gm. of erythromycin was administered every six hours, serum concentrations were rarely lower than 2 γ and were often higher than 10 γ per milliliter. Results of the blood level studies have been reported in detail elsewhere.[3] Representative values are presented in the Chart.

Results of Therapy.—Brief clinical summaries for all 34 patients are presented in Table 2. In general, the patients were only moderately ill, and none were bacteremic. In many of the cases therapy with penicillin, chlortetracycline, or oxytetracycline had been unsuccessful and erythromycin was instituted when it was found that the infecting Staphylococcus was resistant to these three antibiotics.

Evaluation of the results in the 22 patients with soft tissue infections was complicated by the fact that in many cases abscesses were drained and wounds were opened widely. An accurate assessment of the role of the antibiotic in bringing about

recovery was obviously difficult, but in every case there appeared to be improvement which could be attributed to the antibiotic therapy. In most patients the wound was healed within two weeks after therapy was started. It is of interest that in one case (Patient 3) organisms cultured from a large abscess in the right thigh six weeks after therapy was started remained highly sensitive to erythromycin.

Of the 10 patients with osteomyelitis, only 1 seemed to be unimproved by erythromycin therapy. Again, evaluation was difficult because of the other therapeutic measures which were carried out during antibiotic therapy. In general, however, the results were impressive and appeared to be comparable to those which would have been obtained with penicillin if the organisms had been sensitive to this antibiotic. In Patient 24 the infecting organisms were highly resistant to erythromycin after two months of therapy.

The two miscellaneous infections were of unusual interest in that there was an overgrowth of Proteus vulgaris in both cases during therapy, and in one patient this organism was cultured from the blood stream. The patient with secondary staphylococcic pneumonia was the only person who died as a result of staphylococcic infection in the entire series. In this instance therapy with erythromycin was unfortunately stopped when sputum cultures revealed a heavy growth of Proteus vulgaris. At autopsy the internal organs were found to contain many staphylococcic abscesses.

COMMENT

Evaluation of antibiotic therapy of staphylococcic infections is admittedly difficult. The majority of such infections tend to be self-limited, and other therapeutic measures, such as the drainage of abscesses, play an important role in bringing about a cure. Despite these limitations, the results obtained with erythromycin in the present study appeared to be comparable to those observed with penicillin in infections caused by penicillin-sensitive staphylococci. In soft tissue infections fever and toxicity subsided promptly after therapy was begun and the local area of inflammation showed signs of improvement within 24 to 48 hours. These changes were particularly striking in patients who had failed to respond to penicillin, chlortetracycline, or oxytetracycline. In chronic osteomyelitis acute flare-ups were readily controlled and drainage from old sinus tracts diminished but did not disappear. After saucerization of bone and removal of devitalized tissue it was possible in most instances to arrest chronic infections, even when previous attempts had failed. Again, these results appeared to be comparable to those observed a decade ago with penicillin.

There was only one death in the present series which could be attributed to a staphylococcic infection. With the exception of this one case, however, the patients were not suffering from severe staphylococcic sepsis. In the presence of widespread infections, with bacteremia and metastatic abscesses, the mortality rate will undoubtedly remain high despite antibiotic therapy. In a recent study of patients with severe staphylococcic sepsis treated with all the antibiotics currently available, Wise and Spink reported a mortality rate which is still in excess of 50%.[5] Fortunately, such disseminated infections are relatively rare.

5. Wise, R. A., and Spink, W. W.: The Management of Staphylococcal Disease, Bull. Univ. Minnesota Hosp. **24**:645, 1953.

The favorable results obtained in the present series are not surprising in view of the marked sensitivity of staphylococci to erythromycin in vitro and the relatively high blood levels which are easily attainable with this antibiotic. Most staphylococci are inhibited in vitro by less than 0.5 γ per milliliter, and, like penicillin, erythromycin has been found to be bactericidal in its action.[6] When it is administered orally in acid-resistant tablets in doses of 2 gm. daily, serum concentrations ranging from 4 to 20 γ per milliliter are commonly observed.[3] These concentrations are somewhat higher than those obtained with similar doses of penicillin, chlortetracycline, or oxytetracycline. For patients too ill to tolerate oral medications, erythromycin glucoheptonate is well tolerated by the intravenous route and produces high serum concentrations.[7] When administered intravenously, erythromycin tends to disappear from the serum more rapidly than other antibiotics, such as oxytetracycline, but this difficulty can be circumvented by administering larger doses in a continuous intravenous drip.

It has been observed recently, chiefly in staphylococcic endocarditis, that the infecting organisms rapidly become resistant to erythromycin.[8] Development of erythromycin-resistant staphylococci was observed in only one patient in the present study. In most of the cases the organism could not be cultured after the first few days, and therefore follow-up sensitivity studies could not be performed. In three cases, however, organisms were cultured more than three weeks after therapy was started and were found to be sensitive to erythromycin. In all three instances the bacteria were recovered from soft tissue abscesses, and it appears quite possible that contact with the antibiotic is less intimate under these circumstances than in blood stream infections.

Erythromycin was remarkably well tolerated by the oral route. In no instance was it necessary to discontinue the antibiotic because of side reactions. No cases of diarrhea were observed, and in general the patients expressed the opinion that the antibiotic exerted no adverse effects. Even in cases in which erythromycin was given for a period of two months no untoward effects were encountered.

SUMMARY

Thirty-four patients with infections caused by antibiotic-resistant Staph. aureus were treated with erythromycin. Evaluation was difficult in many cases, because other therapeutic measures were carried out simultaneously. In general, however, the response appeared comparable to that observed with penicillin in infections caused by penicillin-sensitive staphylococci.

Initial improvement occurred in 23 patients with soft tissue infections. In 17 the infection was eradicated within two weeks, and periods up to two months were required for healing in 3 others. In three patients relapses occurred when treatment was stopped. Of 10 patients with chronic osteomyelitis, only 1 failed to respond to erythromycin therapy. Acute flare-ups were readily controlled when they occurred,

6. Footnote 2*a*. Haight, T., and Finland, M.: Observations on the Mode of Action of Erythromycin, Proc. Soc. Exper. Biol. & Med. **81**:188, 1952.

7. Maple, F. M.; O'Leary, B., and Kirby, W. M. M.: Serum Concentrations of Erythromycin Following Intravenous Administration, to be published.

8. Finland, M.: Personal communication to the author.

and the chronic infection was arrested or eradicated in eight patients following saucerization of bone and removal of devitalized tissues. In two patients, one with staphylococcic pneumonia secondary to pneumococcic pneumonia and the other with peritonitis, cultures became overgrown with Proteus vulgaris and in one this organism was cultured from the blood stream. The patient with peritonitis eventually recovered, and the one with pneumonia died with multiple staphylococcic abscesses throughout his body.

Prior to therapy, all 34 strains of staphylococci were highly sensitive to erythromycin and were resistant to penicillin, chlortetracycline (aureomycin), and oxytetracycline. In one patient with chronic osteomyelitis of the spine erythromycin-resistant organisms developed after six weeks of therapy. However, in three patients with soft tissue infections the organisms remained sensitive after three weeks of therapy. In the other cases follow-up sensitivity tests were not possible, because the cultures became negative. Erythromycin was well tolerated by the oral route and virtually no side reactions were encountered. Serum concentrations of the antibiotic were remarkably high and well sustained.

EFFECTS OF CORTISONE AND CORTICOTROPIN ON PROLONGED BLEEDING TIME

Treatment in Certain Hemorrhagic States (Pseudohemophilia)

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DURING the past two years there have been observed at the Massachusetts General Hospital a relatively large number of patients with bleeding from various sites in whom there has been found no pertinent organic disease and whose platelets, clotting time, and prothrombin time have been essentially normal. The one defect common to all of these patients is a prolonged bleeding time. The apparent recent increase in frequency of these cases in this hospital can probably be ascribed to improvement in the method of determining the bleeding time. Among many of our patients a history of repeated bleeding episodes over a period of years was noted, but among others such a history was lacking until the present episode.

A number of these patients might be classified as persons with pseudohemophilia.[1] This hitherto rare condition has been thoroughly described in the monographic paper by Estren, Sanchez Médal, and Dameshek,[2] who documented some 62 cases in the previous literature and added a description of 11 of their own cases. In brief, patients with this syndrome include persons of either sex who have a proclivity to bleeding spontaneously or after trauma in the skin, from the mucous membranes, and quite prominently from the uterus. About half of the patients give a family history of bleeding in either sex. The characteristic laboratory findings in pseudohemophilia include a normal number of circulating platelets; a normal or slightly prolonged

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1. The term pseudohemophilia is an unfortunate one, for the condition in patients with the bleeding-time defect, who are the subjects of the present communication, does not resemble hemophilia in either the hereditary aspects, the sex distribution, or in the type of bleeding. Inasmuch as there is no certainty that the condition in these patients conforms to a unitary disease, it is my view that the term "bleeding-time defect" would suffice as a more accurate designation. On the other hand, the term pseudohemophilia has repeatedly been used in the literature, and, as described by Estren, Sanchez Médal, and Dameshek, has come to mean the hemorrhagic disorder that has been variously described in the literature as "hereditary hemorrhagic thrombasthenia," "purpura hemorrhagica without thrombopenia," "hereditary hemorrhagic diathesis," "atypical hereditary hemorrhagic syndrome," and still other terms.

2. Estren, S.; Sanchez Médal, L., and Dameshek, W.: Pseudohemophilia, Blood **1**:504, 1946.

coagulation time, with normal retraction of the clot; a normal or abnormal degree of capillary fragility as estimated by the tourniquet test, but a bleeding time that is usually significantly prolonged.

I have used the following methods for determining the bleeding time. My modification of Duke's procedure [3] consists in sterilizing a No. 11 Bard-Parker blade by soaking in acetone and then drying in the air and similarly sterilizing an ear lobe. With the aid of a tongue depressor held behind the lobe a 2 mm. slash is made through the inferior margin of the lobe so that the blade touches the tongue depressor. With the patient's head in the upright position, the drop of blood is picked off on the rim of a sheet of filter paper at intervals of 30 seconds until the bleeding has ceased, without permitting the paper to come into contact with the incision. By this method the upper limit of normal appears to be five minutes. A modification of the method of Ivy, Shapiro, and Melnick [4] is preferable for repeated testing of the same patient and is illustrated in Figure 1. A forearm is elevated to the same level as the heart, with the patient either reclining or sitting. An area on the volar aspect of the forearm is sterilized with acetone, with avoidance of any visible superficial vein. A sphygmomanometer cuff around the upper arm is inflated

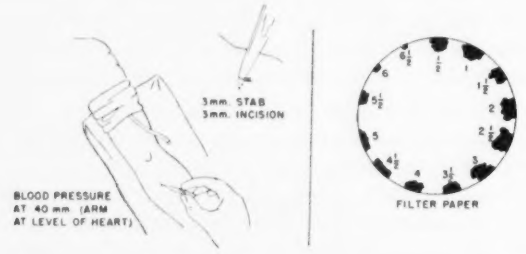

Fig. 1.—Preferred method of determination of the bleeding time.

to 40 mm. of mercury and kept at this level throughout the test. A 3 mm. ink mark is made on the sterilized portion of the forearm and similarly a transverse mark is made 3 mm. from the tip of the acetone-sterilized No. 11 Bard-Parker blade. The blade is thrust into the skin to a depth of 3 mm. and is then drawn distally the length of 3 mm. The arm is tilted so that the drop of blood flows away from the incision and is picked up by the filter paper at intervals of 30 seconds, without the paper touching the incision. By this method the upper limit of normal appears to be six and one-half minutes. The arm method is preferable to the ear method when multiple determinations of the bleeding time are to be performed. It should be emphasized that for each test a new blade is used. Occasionally, even when a superficial vein is not visible, such a vein is accidentally entered, and this is readily evidenced by the fact that the dark venous blood immediately wells up from the wound. Ordinarily, appreciable bleeding from a properly performed incision does not begin until about one minute later, and the blood is bright red.

3. Duke, W. W.: The Relation of Blood Platelets to Hemorrhagic Disease: Description of a Method for Determining the Bleeding Time and Coagulation Time and Report of 3 Cases of Hemorrhagic Disease Relieved by Transfusion, J. A. M. A. **55**:1185, 1910.

4. Ivy, A. C.; Shapiro, P., and Melnick, P.: The Bleeding Tendency in Jaundice, Surg., Gynec. & Obst. **60**:781, 1935.

The suggestion that cortisone might have an influence on menorrhagia accompanied by a prolonged bleeding time was furnished by the following history.

CASE 1.—A 32-year-old woman, first seen on Oct. 11, 1950, was suffering from profuse menorrhagia of six and one-half years' duration, which began after the delivery of her first child. There was no unusual postpartum hemorrhage at this time. The menorrhagia ceased when she became pregnant, some three and one-half years later, and, again, the second delivery was followed by no undue bleeding but the menses returned with the same degree of profuse blood loss. On the supposition that the increased production of corticosteroid hormones in the latter part of pregnancy might be responsible for the absence of postpartum hemorrhage, it was decided to try the effects of such materials in this patient. During five successive menstrual periods, beginning Oct. 21, 1950, control observations revealed the use by the patient of the following number of pads per period, respectively: 48, 32, 46, 56, 60. Two days prior to the next expected period (March 23, 1951) cortisone was given in a dosage of 100 mg. by mouth every eight hours for two successive days and thereafter in decreasing daily amounts. In this period 28 pads were used. During the following period, beginning April 25, 1951, corticotropin (ACTH, Armour) was administered in a dose of 25 mg. intramuscularly every six hours. In this period 65 pads were used. Finally, during the following period, beginning May 28, 1951, administration of cortisone was resumed, with use of a total of 32 pads.

This suggestive hemostatic influence of cortisone has been studied in 18 additional cases.[5] All 18 patients are described in the accompanying Table. To these patients cortisone was administered almost entirely orally, usually initially in a dose of 300 mg. daily during the first few days, until the bleeding time had fallen significantly, and thereafter the daily dose was progressively decreased. The period of administration of the drug averaged nine days in most instances. In only one instance (Case 2) the material was administered over a period of 22 days. In Figure 2 are depicted the results of determinations of bleeding times in 25 trials among 19 patients.

It can be seen from these data that after the administration of cortisone the bleeding time in most patients fell significantly after two days of treatment and in all but three instances reached a normal value after four days of treatment. In Case 1 the patient underwent extensive surgical treatment of severe varicose veins with no abnormal bleeding. In Case 3 the patient bled extensively after cholecystectomy in April, 1951, at a time when the bleeding tendency was not recognized preoperatively, but after preparation with cortisone in May, 1953, she experienced no abnormal bleeding following repair of an enterocele. In Case 4 an osteotomy of each knee during two separate operations was performed, with no undue bleeding. In Case 7 the patient initially had 2 teeth extracted, with no significant bleeding, and then three weeks later underwent extraction of 21 teeth, under general anesthesia, with no abnormal bleeding, despite the fact that, as seen in Figure 2, the bleeding time on each of the two occasions receded from the initial level but did not reach a normal value. In Case 12 extensive extractions of teeth and surgery of the gums were performed with no abnormal bleeding. Finally, in Case 19 the patient bled excessively after tonsillectomy in 1946, but in May, 1953, after preparation with cortisone, she underwent a hysterectomy with no undue bleeding. Among the remaining cases, hemorrhage, when already present, apparently diminished within

5. The following members of the staff of the Massachusetts General Hospital referred the patients described in the Table: Drs. Arthur W. Allen, Maurice Fremont-Smith, Robert L. Goodale, Walter C. Guralnick, Edgar M. Holmes, Vincent J. Kelley, Moses H. Lurie, Joe Vincent Meigs, Maurice R. Ruben, Howard Ulfelder, George Van Gorder, and Claude E. Welch. The Medical Officer in Command and the members of the Medical Service of the United States Naval Hospital, Chelsea, Mass., placed at our disposal Cases 17 and 18.

Case No.	Sex	Age, Yr.	Date of Observation	Family History	Past History	Present Illness
1	F	32	1950-1951	Negative	Menorrhagia since 1st delivery 6½ years ago; no postpartum bleeding 6½ and 1½ years ago; nosebleeds in childhood; ease of bruising, many years; bleeds easily from cuts	Menorrhagia
			1952	.....	.....	Preparation for bilateral vein operations
2	F	75	4/51 to 12/51	Negative	Negative	Epistaxis
			12/51	.....	.....	Epistaxis
3	F	54	4/51	Uncertain	Ease of bruising, for years; hysterectomy for menorrhagia 18 years ago	Bleeding from incision after cholecystectomy
			5/53	.....	.....	Preparation for excision and repair of enterocele
4	M	21	2/51	Negative	Negative	Bleeding from attempted osteotomy
			5/51	.....	.....	Trial of cortisone
			6/51	.....	.....	Osteotomy right knee
			7/51	.....	.....	Osteotomy left knee
5	M	17	6/51	Maternal grandfather a "bleeder," with mildly prolonged bleeding time and clotting time	Bleeding from tooth socket in 1946	Massive subgaleal hematoma after trauma
6	F	51	7/51	Negative	Always bruised easily; menorrhagia; severe recurrent epistaxes, few years	Epistaxis
7	F	19	9/51	Negative	Always bruised easily; bleeding after adenoidectomy 6 years ago and after appendectomy 8 months ago; bled after extraction of tooth, 10 days ago; no menorrhagia; frequent epitaxes	Preparation for extraction of 2 teeth
			10/51	.....	.....	Preparation for extraction of 21 teeth
8	F	38	10/51	Negative	Numerous bleeding episodes since age 10	Bleeding from vaginal cuff after hysterectomy
9	M	25	7/52	Negative	Bled 1 week after tonsillectomy at 15	Bleeding after rhinoplasty, for 7 days
10	M	20	10/52	Negative	Frequent epistaxes, few years	Epistaxis
11	M	18	7/52	Negative	Negative	Bleeding after submucous resection
12	F	29	3/53	Negative	Bruises easily, for years; severe bleeding after extractions, 2 years ago; no menorrhagia	Preparation for multiple tooth extractions and alveoplasty
13	M	42	11/52	Negative	Negative	Epistaxis
14	F	20	12/51	1 brother has "pseudohemophilia"	Previously diagnosed "pseudohemophilia"; ease of bruising and from cuts, since childhood; menorrhagia; severe postpartum bleeding after only delivery	Menorrhagia
			2/52	.....	.....	Menorrhagia
15	M	3 mo.	11/51	Mother has "pseudohemophilia"	Vomiting since birth, with hematemesis	Preparation for pyloromyotomy
16	M	43	2/53	Negative	Negative	Epistaxis
17	M	24	4/53	Father bleeds easily, epistaxes in 1 brother and sister	Bruises easily, for years; bleeds easily when cut; severe bleeding after 2 extractions, last 7 years	Bleeding after extraction of 2 teeth
18	M	19	3/53	Sister's son is a bleeder	Bleeding tendency 7 years; 3 extractions followed by severe bleeding; frequent epistaxes for 3 months	No bleeding at present
19	F	34	1/53 to 5/53	Father and paternal grandfather "bleeders," 1 sister bruises easily	Tonsillectomy in 1946 with excessive bleeding; always bruised easily; 4 separate dental extractions with excessive bleeding, last 1939; recurrent epistaxes; menorrhagia since 1946; D & C in 1949 negative	Preparation for hysterectomy (fibroids)

* Corticotropin given intravenously in daily dose of 20 to 25 mg.
† Corticotropin given subcutaneously.

Bleeding Time, Min.	Clotting Time	Clot Retraction	Prothrombin Time	Platelets	Capillary Fragility	Treatment Days, No.	Total Dosage of Cortisone, Mg.	Comment
14½	Normal	Normal	Normal	Normal	Increased	.	.....	Menorrhagia markedly lessened by cortisone during 2 periods; normal delivery with no postpartum bleeding 3/8/52
10								
7								
12								
During pregnancy 7								
During pregnancy 6½								
During pregnancy 5								
During pregnancy 4½								
During pregnancy 7½								
22½+	.....	.....	.....	.....	.....	11	2,150	Bilateral stripping long saphenous veins, ligation short saphenous veins, followed by no abnormal bleeding
20+	Normal	Normal	Normal	Normal	.....	22	4,000	Improved on cortisone
20+	.....	.....	Normal	Normal	.....	16	2,650	Improved on cortisone
12½+	Slightly prolonged	Normal	75%	Normal	.....	5	1,325	Improved (mild agitation from cortisone on 5th day)
15½	Normal	Normal	63%	Normal	.....	12	2,600	No abnormal bleeding
9	Normal	Normal	Normal	Normal	Normal	..	.....	Fibrinogen and prothrombin consumption normal; no effect of fresh blood transfusion on bleeding time
14½								
15								
						10	2,250	.....
21+	.....	.....	.....	.....	.....	7	1,150	No abnormal bleeding
8	.....	.....	.....	.....	.....	10	1,800	No abnormal bleeding
13½	.....	.....	.....	.....	.....	7	1,600	No effect of transfusion on bleeding time; improved; scalp drained
10½	Prolonged, brought to normal by fresh blood transfusion	Normal	62%	Normal	.....			
12½								
16½	Normal	Normal	.....	Normal	.....	11	2,175	Improved
19	Normal	Normal	Normal	Normal	Increased	5	900	No abnormal bleeding
21+	.....	.....	.....	.....	.....	6	1,400	No abnormal bleeding
12	Normal	Normal	75%	Normal	Increased	6	1,175	Improved
10+	Normal	Normal	Normal	Normal	.....	11	2,225	Improved
9½	Normal	Normal	70%	Normal	.....	6	1,250	Improved
10½								
21	Normal	.....	Normal	Normal	.....	7	1,550	Improved
20+	Normal	Normal	Normal	Normal	.....	10	2,500	No abnormal bleeding
9	Normal	Normal	Normal	Normal	.....	13	2,225	Improved
40	Normal	.....	Normal	Normal	Increased	9	4,100	No change after cortisone
60+	.....	.....	.....	.....	.....	8	175*	No change after corticotropin
35+	Normal	.....	.....	Normal	.....	7	102†	No abnormal bleeding after corticotropin
11½	Normal	.....	Normal	Normal	.....	6	1,100	Improved
13	Normal	.....	.....	.....	.....	11	2,500	Improved
21	Slightly prolonged	.....	Normal	Normal	.....	8	1,950	Prothrombin consumption normal
10	Normal	Normal	Normal	Normal	.....	14	3,050	No abnormal operative or postoperative bleeding
12½								
21½								

72 hours. A few observations revealed a return of the bleeding time to high levels within 48 hours after cessation of the administration of cortisone (Fig. 2). An exception to the above remarks is Case 14. In this case large amounts of cortisone or of corticotropin produced no apparent effects whatever on the bleeding time.

That corticotropin may duplicate the effects of cortisone is indicated by the following observations, which were made by Dr. Robert E. Gross, Chief of the Surgical Service, Children's Medical Center, Boston. A 3-month-old boy (Case 15), whose mother had previously been classified as a pseudohemophiliac, suffered

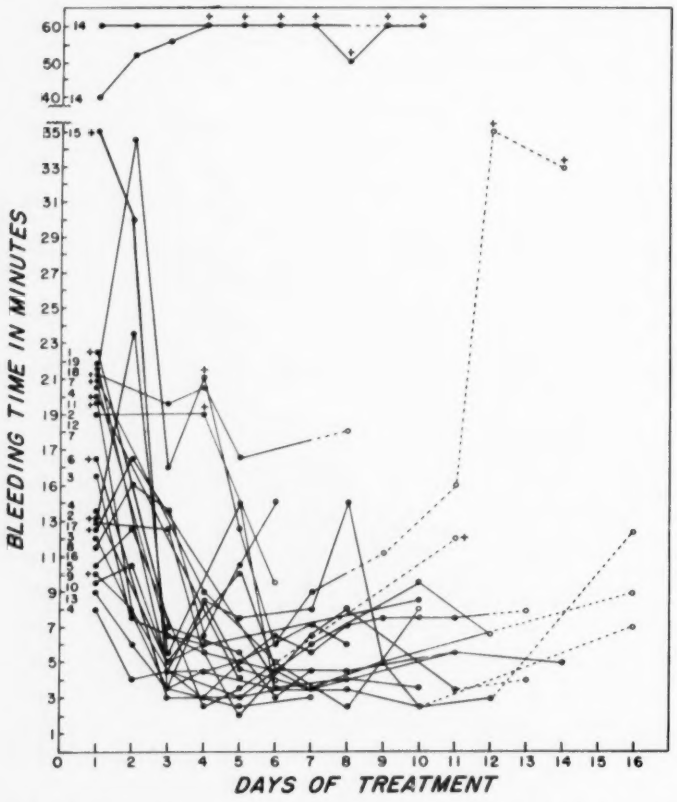

Fig. 2.—Effect of cortisone and of corticotropin on the bleeding time in pseudohemophilia. The numeral to the left of each curve refers to the case number in the Table. The symbol + adjacent to any point on a curve indicates that the bleeding time end-point was not determined. The upper curve of Case 14 and curve of Case 15 represent the effects of corticotropin; all other curves represent the effects of cortisone. The dotted portion of each curve represents the bleeding time after the daily dose of cortisone was reduced to less than 75 mg.

from pseudohemophilia and pyloric stenosis and was prepared for pyloromyotomy by means of administration of corticotropin (Wilson) during a period of 48 hours, preoperatively, receiving 0.125 cc. intramuscularly every 6 hours. During this period the bleeding time fell from approximately 30 minutes to 2½ minutes. The operation was performed with no abnormal bleeding and was followed by no post-

operative bleeding. The drug was continued in decreasing doses for four days postoperatively. Nine days postoperatively the bleeding time had risen again to the preoperative level (Fig. 2).

COMMENT

The mechanism of the action of cortisone is not apparent; on the other hand, the mechanism of the bleeding time defect in pseudohemophilia remains obscure.[2] Of interest, however, are the observations of Robson and Duthie,[6] who found a marked decrease in capillary permeability among nonbleeding patients following the administration of corticotropin. Similar changes in the blood vessels of the rabbit ear have been reported by Ebert,[7] and changes in vascular fragility in vascular purpura have been described in one case by Stefanini and co-workers[8] and in four cases of thrombopenic purpura by Faloon and others.[9] I made very similar observations in a previous study of the effects of corticotropin and of cortisone in idiopathic thrombopenic purpura.[10] It appears very likely, therefore, that the action of cortisone on the bleeding time in patients with a prolonged bleeding time is a nonspecific effect.

SUMMARY

Eighteen adults with prolonged bleeding time were treated with cortisone, and one infant was treated with corticotropin. In every instance but one the administration of the drug was followed by a decrease in the bleeding time and by the prevention, or the cessation, of hemorrhage.

6. Robson, H. N., and Duthie, J. J. R.: Capillary Resistance and Adrenocortical Activity, Brit. M. J. **2**:971, 1950.

7. Ebert, R. H.: Changes in Connective Tissue Reaction Induced by Cortisone: In Vivo Observations Using Rabbit Ear Chamber Technique, J. Clin. Invest. **30**:636, 1951. Ebert, R. H., and Wissler, R. W.: In Vivo Observations of the Effects of Cortisone on the Vascular Reaction to Large Doses of Horse Serum Using the Rabbit Ear Chamber Technique, J. Lab. & Clin. Med. **38**:497, 1951.

8. Stefanini, M.; Roy, C. A.; Zannos, L., and Dameshek, W.: Therapeutic Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in a Case of Henoch-Schönlein Vascular (Anaphylactoid) Purpura, J. A. M. A. **144**:1372, 1950.

9. Faloon, W. W.; Greene, R. W., and Lozner, E. L.: Hemostatic Defect in Thrombocytopenia as Studied by the Use of ACTH and Cortisone, J. Clin. Invest. **30**:638, 1951.

10. Jacobson, B. M., and Sohier, W. D.: Effects of ACTH and of Cortisone on the Platelets in Idiopathic Thrombopenic Purpura, New England J. Med. **246**:247, 1952.

STUDIES ON HEADACHE

Evidence of Tissue Damage and Changes in Pain Sensitivity in Subjects with Vascular Headaches of the Migraine Type

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NEW YORK

TO ASCERTAIN whether the cranial vascular functions of subjects with vascular headache are in any way different from those of subjects without headache, cranial artery pulse wave contour records were obtained two to five times weekly on 40 subjects with vascular headaches of the migraine type. These were taken both during headache and in headache-free phases over a period of one to six months. Such records were contrasted with records similarly taken on 10 subjects who never or but rarely had headaches.[1]

It became evident that even during headache-free phases the person who is subject to vascular headaches exhibits significantly greater variation in the contractile state of certain parts of the cranial vascular tree than does a person who is not subject to headache. Such variability in the headache-free phase is especially evident during those periods of life that are marred by severe and frequent attacks. About 72 hours prior to the onset of headache this variability is increased. Twenty-four hours prior to headache variability is featured by periods of more vasoconstriction, frequently maximal during the minutes preceding the onset of headache. During the headache attack there is vascular dilatation and distention and intramural edema of relevant vessel walls.

It was inferred that the striking modifications in vascular function characteristic of the headache attack itself merely punctuate a series of changes that are more or less continuously a feature of the life adjustment of those persons subject to vascular headache.

More specifically, changes in contour of pulse waves recorded from cranial arteries during the vascular headache attack provide evidence of an altered contractile state, predominantly distention.[2] Also, changes consistent with increased

From The New York Hospital and the Departments of Medicine (Neurology) and Psychiatry, Cornell University Medical College.

1. Tunis, M. M., and Wolff, H. G.: Studies on Headache: Long-Term Observations of Alterations in Function of Cranial Arteries in Subjects with Vascular Headache of the Migraine Type, Program of the 78th Annual Meeting of the American Neurological Association, Atlantic City, June 15-17, 1953, P. 24.

2. Wolff, H. G., and Tunis, M. M.: Analysis of Cranial Artery Pressure Pulse Waves in Patients with Vascular Headache of the Migraine Type, Tr. A. Am. Physicians **65**:240, 1952.

vascular resistance and edema were noted. Moreover, changes compatible with edema of the vascular walls were found on palpation and inspection. Furthermore, in another vascular bed, i. e., that of the bulbar conjunctivae, a similar altered state during headache was observed. Thus, the arterioles, capillaries, and venules, examined by a slit lamp in the eyes of 20 subjects during headache attacks, exhibited on the headache side a greatly increased diameter. However, in contrast with analogous vessels on the contralateral side, the blood flow rate was reduced as much as fivefold.

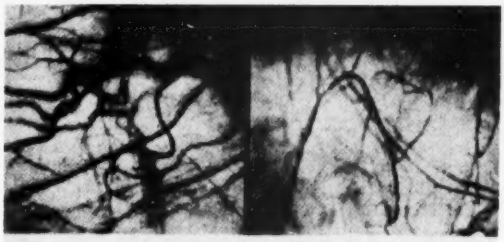

Fig. 1.—Contrast in appearance of vascular structures in right and left bulbar conjunctivae during right-sided headache. Conjunctival vessels in the eye on the headache side are increased in diameter and exhibit great tortuosity. On inspection through the slit lamp the walls of these vessels are "blurred"; there are relatively few red cells within their lumina, and blood flow is slow.

Hematomata with Migraine Headache

Patient	Sex	Age, Yr.	Hours of Headache Prior to Hematoma	Intensity of Headache*	Site of Hematoma	Previous Hematomata, No. and Site
F. R.	F	48	60	10	Temporal, L	2, L
J. C.	F	32	36	8	Temporal, R	1, L
C. R.	F	31	28	6	Temporal, R	....
D. I.	M	32	30	6	Preauricular, R	....
M. G.	F	42	48	10	Temporal, L	1, R
A. M.	M	65	18	9	Temporal, R	1, L
K. L.	M	64	42	10	Preauricular, L	1, L
C. M.	F	53	12	10	Preauricular, R	....
B. L.	F	47	28	10	Preauricular, L	1, R
B. R.	F	46	18	8	Temporal, L	....
S. C.	F	62	32	10	Temporal, R	1, R

* Intensity of headache is expressed in arbitrary units, indicating in each instance the patient's own evaluation of his pain in terms of past headache experience. A unit here is not the equivalent of a "dol" (Hardy, J. D.; Wolff, H. G., and Goodell, H.: Studies on Pain: Measurements of Aching Pain Threshold and Discrimination of Differences in Intensity of Aching Pain, J. Appl. Physiol. 5:247, 1952; Studies on Pain: Discrimination of Differences in Intensity of a Pain Stimulus as a Basis of a Scale of Pain Intensity, J. Clin. Invest. **26**:1152, 1947; Pain Sensations and Reactions, Baltimore, Williams and Wilkins Company, 1952).

This was estimated by the time taken for a single red blood cell in the lumen of a minute vessel to traverse a measured distance in the eyepiece of the slit lamp.[3]

In addition to the vascular structures, other tissues on the outside of the cranium were often observed to be edematous. Moreover, they were tender on palpation, especially tissues adjacent to painful and tender vascular structures.

3. Observations made through the courtesy of Dr. Richard E. Lee, Department of Medicine, Cornell University Medical College.

Conspicuous evidence of damage to vascular walls during headache was 19 spontaneous hematomata in areas of headache in 11 patients during 19 attacks of migraine. The hematomata varied in diameter from 1 to 6 cm. and in depth from 0.5 to 2 cm. They were usually localized in the tissues adjacent to the frontal branch of the involved temporal artery and made their appearance in 10 to 60 hours after

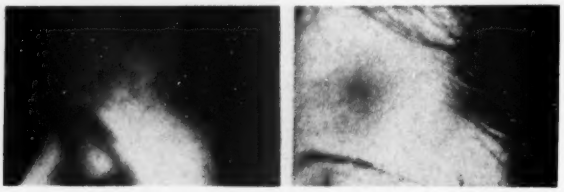

Fig. 2.—Two views of a hematoma about the left temporal artery that developed 48 hours after onset of headache in subject M. G. (see Table).

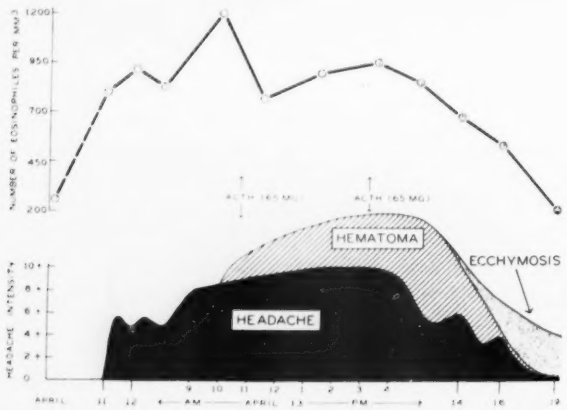

Fig. 3.—Demonstration of the time of onset and development of a hematoma during a severe long-lasting migraine headache attack. It is doubtful whether the corticotropin (ACTH) in this instance altered the course of events.

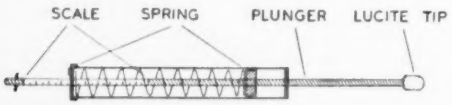

Fig. 4.—Diagram showing the principle of the Hardy deep pain dolorimeter. The lucite tip is placed on the test site, and pressed against the subject's head at a standard rate. The pain threshold is expressed as the number of units representing grams of pressure of the coiled spring when the subject first perceives deep aching pain.

the onset of a severe headache attack. The hematomata were tender on palpation and ecchymotic in appearance and persisted for a few days to over a week.

Also evidence of tissue damage, although far less dramatic than such relatively rare hematomata, is the tenderness of tissues on the outside of the cranium, long recognized as a common feature of vascular headaches involving extracranial

arteries. It has been suggested that such hypersensitivity may be a factor in the mechanism of headache, since vasodilation per se does not always induce headache. Experiments were designed to explore this thesis.

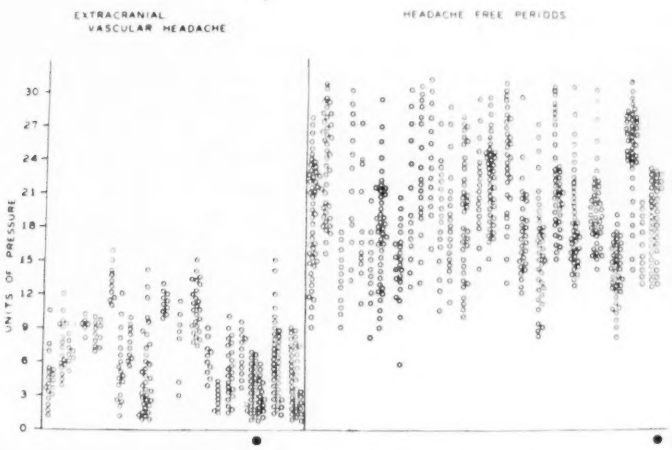

Fig. 5.—Deep pain threshold measurements made in the zone of headache during migraine attacks in 10 subjects compared with deep pain thresholds during headache-free periods. The two black dots identify measurements in one person.

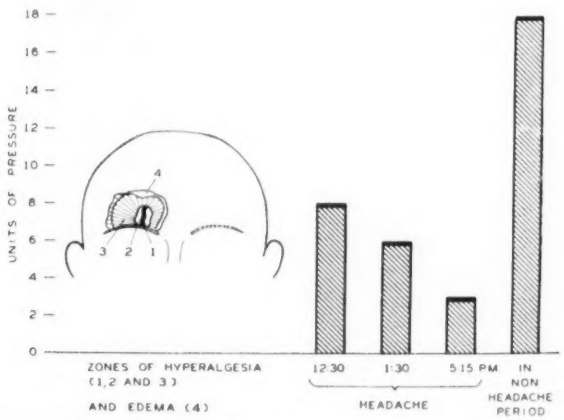

Fig. 6.—Progressively lowered thresholds of deep pain during supraorbital vascular headache. Demonstration of the zone of maximal pain intensity and lowest deep pain threshold over the supraorbital artery (*1*). Pain threshold was lowered in adjacent tissues (*2*, *3*) as headache continued. Note also that the pain threshold was progressively lowered in Zone 1 as headache continued.

METHOD

A recently developed appartus was used to assay deep pain thresholds, and the Hardy-Wolff-Goodell dolorimeter was used to measure superficial pricking pain thresholds. Measurements were made at 42 sites distributed over the frontal, supraorbital, and temporal areas on both sides of the head.

RESULTS

A. Initially it was demonstrated that dilatation of the superficial temporal, supraorbital, and frontal arteries following exposure to ultraviolet radiation and after iontophoresis of acetylcholine or histamine did not in itself induce headache or lower deep pain thresholds, although lowered threshold for superficial pain ensued. Similarly, procedures that moderately increased intravascular pressure in these dilated arteries, such as tilting to the head-down position and performing strenuous exercise, did not induce headache. Local swelling produced by infiltration of the subcutaneous tissues of the head with isotonic sodium chloride solution had no pain-threshold-lowering effect, nor did it induce headache, except that resulting from the process of injection.

B. Daily pain threshold measurements were made over a period of months in a series of 10 patients who had at intervals vascular headache involving extracranial arteries. Approximately 1,000 measurements taken during the headache-free phases

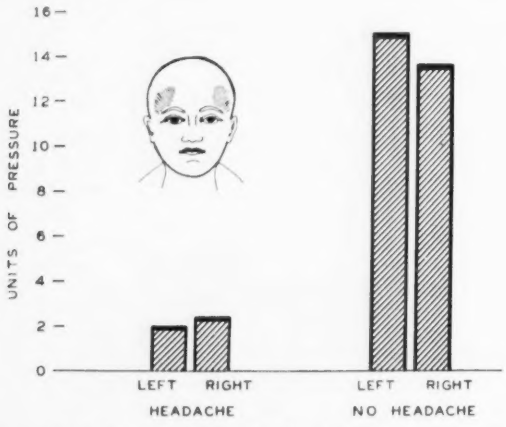

Fig. 7.—Demonstration of lowered deep pain threshold over the temporal artery and in adjacent tissues in a subject with bitemporal vascular headache.

were then compared with approximately 800 taken during headache attacks (measurements totaling approximately 500 were made less frequently in nine other patients during headaches and on headache-free days). It was demonstrated that during the headache-free periods the deep pain thresholds were high and predictable. During headaches the deep pain threshold of the cranial tissues was low, being maximally lowered in the zone of headache. Initially this zone of low threshold was circumscribed, but subsequently it became more widespread, commonly outlasting the headache by hours or even days. Occasionally, after prolonged headaches, lowered thresholds were evident for as long as six days. Further, deep pain thresholds in some persons during hemicrania were slightly low on the nonpainful or less painful side of the head. The deep pain threshold was lowered progressively as the headache continued and worsened. At the onset of headache the zone of hyperalgesia was always focal and circumscribed in the area of headache. The deep tissues near or over arteries and possibly veins were especially sensitive, and a major lower-

ing of pain threshold was associated with the most intense, often sharply localized, headaches. During a period when headache attacks were frequent, slight lowering of the pain thresholds was noted during headache-free phases, in association with moderate cranial artery vasodilatation.

On the other hand, during periods of freedom from headache in subjects with infrequent headaches deep pain threshrolds measured at hourly intervals before, and as late as one hour before, the onset of headache were not conspicuously lowered. This indicates that the lowered pain threshold although outlasting the attack did not long precede it and hence was probably an accompaniment of the attack. The superficial pricking pain threshold of the skin was not significantly lowered, although superficial "secondary hyperalgesia" [4] usually accompanied the lowered deep pain thresholds.

C. Headache due, at least in good part, to noxious stimulation of pain-sensitive intracranial structures was in some instances also accompanied by lowered deep pain threshold of extracranial tissues. However, such areas of reduced threshold

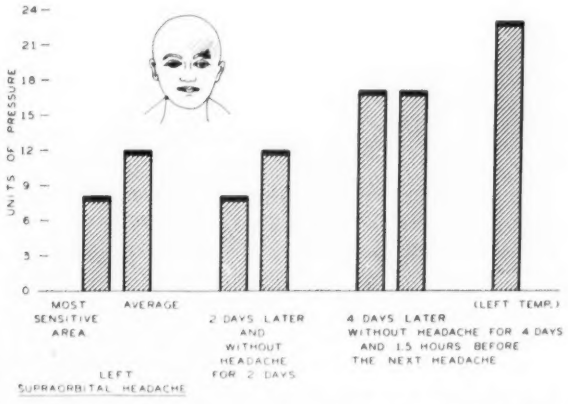

Fig. 8.—Demonstration of the persistence of low deep pain thresholds in the left supraorbital region in a subject with left supraorbital headache. In this instance lowered deep pain thresholds outlasted the headache for four days. Note also that the threshold was moderately high just before the onset of a second attack.

were not as focal or circumscribed as those associated with extracranial vascular headaches. Also, extracranial tenderness accompanying headaches primarily from intracranial sources usually developed after some hours or days of headache. It is possible that the lowered deep pain thresholds resulted from secondary involvement of the extracranial vessels. This topic is being further explored.

SUMMARY AND CONCLUSIONS

During the examination of a large group of persons experiencing vascular headache of the migraine type, spontaneous hematomata in the temporal and preauricular regions in 11 subjects were observed, providing evidence of gross tissue injury in

4. "Secondary hyperalgesia" is the situation in which there is no lowering of the pain threshold but there is intensification of pain sensation at or above the threshold of stimulation of pain.

the area of headache. Repeated observations on a series of 19 subjects with headache who did not have hematomata at the time revealed that lowered deep pain threshold about the extracranial arteries and adjacent tissues was an invariable accompaniment of the headache. Neither lowered threshold alone nor moderate vasodilatation, per se, caused headache, yet alteration in the contractile state of the cranial arteries was an essential requirement. Further, those persons subject to vascular headache exhibited a heightened variability in the contractile state of specific portions of the cranial vascular tree, which was especially notable during periods of frequent attacks. At such times, after a period of conspicuous variability in contractile state of cranial arteries, there followed a phase of vasoconstriction succeeded by dilatation, intramural vascular edema, and lowered pain threshold. Under these circumstances vasodilatation becomes painful and the headache attack ensues.

CHLORTETRACYCLINE (AUREOMYCIN) IN PREVENTION OF BACTEREMIA FOLLOWING ORAL SURGERY

Attempt to Prevent Subacute Bacterial Endocarditis in Patients with Heart Disease

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ANYBODY with a heart murmur, whether it is due to rheumatic, syphilitic, congenital, or arteriosclerotic heart disease, is a potential candidate for subacute bacterial endocarditis, although only a small percentage of persons actually become affected by this disease. Nineteen patients suffering from subacute bacterial endocarditis were admitted in the years 1947 through 1949 to the New Haven Hospital, only one of three general hospitals in this community.

Subacute bacterial endocarditis is still a formidable disease, despite a great advance in treatment with antibiotics, in particular penicillin. In 1940, in the prepenicillin era, 45 persons in Connecticut and 2,531 in the entire United States were reported to have died from subacute bacterial endocarditis. In 1949, when penicillin was readily available for therapy, 10 persons in Connecticut and 1,187 in the entire nation died of this disease, according to the Bureau of Vital Statistics.[1] The actual figures are probably much higher, since subacute bacterial endocarditis is often not recognized. The number of patients treated yearly for this disease is not known, as subacute bacterial endocarditis is not a reportable illness, but it is surely many times higher than the number of fatalities. Formerly an almost 100% fatal disease, it is successfully arrested now in about 90% of cases, while in 10% all treatment is resisted and active valvular vegetations are shown on postmortem examination. Another 10 to 20% of patients, however, despite the clinical cure of the infection, die of the complications of the disease itself, such as heart failure, uremia, and emboli. This is explained by the fact that penicillin alone or in conjunction with other antibiotics is capable of healing an infection but is unable to prevent a subsequent deterioration of the heart, particularly if the treatment is not instituted promptly. In view of the fact that the mortality is still high and that, even in suc-

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1. Harnszel, W.: Personal communcations to the authors.

cessful cases, the long treatment is extremely expensive and causes severe economic hardship, it is of utmost importance to prevent subacute bacterial endocarditis.

About 20 to 25% of all patients with subacute bacterial endocarditis give a history of having had oral or other surgery performed shortly before the onset of the disease. Since bacteremia immediately following the surgical procedure, transient as it may be, is the presumed cause of subacute bacterial endocarditis in patients with previous cardiac disease, it was felt that if this bacteremia could be prevented the incidence of subacute bacterial endocarditis in patients with cardiac disease could be decreased.

This was achieved in a high percentage of patients with penicillin alone or with penicillin and sulfisoxazole (Gantrisin) combined, as was shown in excellent studies by Rhoads and his co-workers,[2] Glaser and his co-workers,[3] and Hirsh and others.[4] Penicillin, however, often causes allergic reactions and is reliable only when given by injection. Dentists and patients often shy away from these injections and therefore prophylactic use of penicillin is often omitted, at times with fatal consequences.

For these reasons chlortetracycline (aureomycin),[5] a broad-spectrum antibiotic, was selected. It can be given successfully by mouth, is relatively less toxic, and does not lead to development of resistant organisms. In an attempt to establish the effectiveness of chlortetracycline in averting the transient bacteremia following oral surgery a previous study [6] revealed that of 25 patients without heart murmurs given prophylactically 2 gm. of chlortetracycline per day in divided doses, the day before, the day of, and the day after the operation, only one patient showed a positive blood culture for a viridans Streptococcus. This is an occurrence rate of 4%. The one patient with a positive culture was given the last dose of chlortetracycline by error four and one-half hours prior to the operation instead of two hours before, which seems to be preferable. In a control group of 25 patients, also without heart disease, in whom the extent of oral surgery and infection was even less than that of the treated group, 78% showed a positive blood culture of various organisms immediately after oral surgery. Of these 25 patients, 56% showed a growth of a viridans Streptococcus, the commonest cause of subacute bacterial endocarditis. Cultures of materials taken before extraction and ½ hour and 24 hours after extraction were negative for all 50 patients, demonstrating the short duration of the postoperative bacteremia. This result, which compared favorably with results obtained with penicillin alone or with penicillin and sulfisoxazole, convinced us of the effectiveness of chlortetracycline in the prevention of bacteremia following oral surgery.

The present report deals with chlortetracycline treatment of 20 adult patients with known organic heart murmurs of various causes for whom oral surgery was

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5. Chlortetracycline (aureomycin) was supplied by J. M. Ruegsegger, M.D., Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

6. Roth, O.; Cavallaro, A. L.; Parrott, R. H., and Celentano, R.: Aureomycin in Prevention of Bacteremia Following Tooth Extraction, Arch. Int. Med. **86**:498 (Oct.) 1950.

performed. The age range of these patients with cardiac disease is comparable to that of the patients without cardiac disease previously treated. It was considered important to test the efficacy of the therapy in preventing bacteremia in patients with cardiac disease, as theoretically it is possible that chlortetracycline, a bacteriostatic agent, might prevent multiplication of bacteria in the blood stream after surgery sufficiently to give a temporarily negative blood culture but that after its action had subsided a few surviving bacteria could settle on a damaged valve and multiply and cause subacute bacterial endocarditis. In addition to this, it was felt that any increase in the number of treated patients would further help to determine whether chlortetracycline was effective in preventing bacteremia following oral surgery.

It was recognized that this method of study, considering the few patients with cardiac lesions treated, could not establish whether the incidence of subacute bacterial endocarditis was reduced. However, it was reasoned that if the bacteremia following oral surgery could be abolished one could assume, although not prove, that subacute bacterial endocarditis would not follow.

Incidence of Cultures of Blood Drawn Immediately After Tooth Extraction Which Were Positive for Viridans Type of Streptococcus in Control and Treated Patients According to Dental Classification

	Untreated Patients Without Heart Disease			Treated Patients					
				Without Heart Disease			With Heart Disease		
Dental Class	No.	Str. Viridans in Blood	% of Total Patients	No.	Str. Viridans in Blood	% of Total Patients	No.	Str. Viridans-Type in Blood	% of Total Patients
I.....	1	1	4	1	0	0	0	0	0
II.....	8	5	20	7	1	4	1	0	0
III.....	10	6	24	7	0	0	9	0	0
IV.....	6	2	8	10	0	0	10	0	0
Total.....	25	14	56	25	1	4	20	0	0

METHOD OF STUDY

All patients were operated upon at the hospital, either as outpatients at the clinic or as inpatients in the ward. Only adult patients with organic heart murmurs were selected for this study. Of the 20 patients treated, 12 were afflicted with rheumatic, three with congenital, and five with hypertensive-arteriosclerotic heart disease. Oral surgery and infection varied from the extraction of one tooth to the extraction of all teeth and trimming of the gums. The patients were classified in four classes according to the amount of infection and necessary surgery.[6] Thirteen patients received general anesthesia with intravenous thiopental (Pentothal) sodium, and the remaining 7 patients were operated upon under local anesthesia, depending on the number of extractions to be performed and the state of the cardiac compensation. Three of the patients who received local anesthesia were given procaine without epinephrine (Adrenalin) because of marked hypertension and coronary artery disease. Prior to surgery all the patients received four doses of 500 mg. chlortetracycline with milk every six hours, the last dose being given exactly two hours before surgery. After the operation the schedule of 500 mg. of chlortetracycline every six hours timed from the last dose was continued until a total of 3 gm. had been given. All the patients were carefully instructed to continue the medication even in case of nausea, a side-reaction sometimes seen with chlortetracycline. Prior to the first dose of chlortetracycline, immediately before and after the operation, half an hour later, 24 hours later, and 4 weeks later blood was taken for culture. The blood was cultured in broth and on pour plates exactly as described previously[6] and the cultures were kept for four weeks. At the four week follow-up examination the patient was also carefully questioned for symptoms and examined for signs of subacute bacterial endocarditis.

RESULTS

None of the 20 patients with heart disease treated with chlortetracycline had any detectable bacteremia before surgery, immediately after, or ½ hour, 24 hours, or 4 weeks later. Nor did any at the time of follow-up, four weeks after surgery, have any signs or symptoms suggestive of subacute bacterial endocarditis. The majority of these patients were seen again several months after oral surgery and were found to be free of subacute bacterial endocarditis. All the patients showed good and prompt healing of the gums.

COMMENT

The result of these studies on patients with cardiac disease confirmed our previous findings on patients without heart disease that chlortetracycline is effective in preventing bacteremia following oral surgery. It was gratifying to notice that many of the patients with cardiac disease presented themselves to us with the request for antibiotic prophylaxis prior to oral surgery, giving proof of the value of instructing every patient at the time the organic heart murmur is first detected that he request such treatment when oral surgery is planned. This, however, should not decrease one's vigilance in examining patients carefully prior to oral surgery for organic heart murmurs, even if a carefully taken history reveals no rheumatic fever, chorea, syphilis, or arteriosclerotic or congenital heart disease in the past.

The importance of the prophylactic use of antibiotics—in our study, chlortetracycline—becomes obvious if one compares the occurrence rate of bacteremia in treated and untreated patients and if one remembers that about 20 to 25% of patients with subacuate bacterial endocarditis give a history of having had such procedures performed without prophylactic use of antibiotics. In our series of 45 treated patients, 20 with heart disease and 25 without, only one patient without heart disease had a positive blood culture following oral surgery. This is an incidence of only 2.2%. Of 25 patients without heart disease who did not receive chlortetracycline 14, or 56%, showed positive cultures for viridans streptococci. Every patient with heart disease received a careful examination four weeks after surgery, including a blood culture. This postoperative examination of patients with heart murmurs is, in our opinion, of the utmost importance in detecting and treating subacute bacterial endocarditis early, should it occur despite prophylactic use of chlortetracycline, as early treatment greatly enhances the chance of survival. It might be of interest to note that one of the patients had been previously successfully treated for subacute bacterial endocarditis.

Chlortetracycline caused nausea and occasional vomiting in some of the patients. The occurrence and severity of it were greatly reduced by giving milk and, at times, dimenhydrinate (Dramamine), 50 mg. at the same time. It seemed wise, however, to inform the patient of the possibility of such a side-reaction and to stress the importance of continuing the medication exactly at the specified time.

SUMMARY AND CONCLUSION

Twenty adult patients with organic heart disease due to various causes were treated with 2 gm. of chlortetracycline (aureomycin) daily in four divided doses on the day before, the day of, and the day after surgery. The last preoperative dose of 0.5 gm. of chlortetracycline was given two hours prior to surgery to assure high blood levels at the time of possible bacteremia immediately following extraction.

Blood cultures taken before onset of therapy, immediately before and after surgery, half an hour later, 24 hours later, and 4 weeks later were sterile. The results obtained in this study give additional support to our previously reported findings [6] on 25 patients without heart disease, that chlortetracycline used prophylactically is successful in greatly reducing bacteremia following oral surgery. The fact that blood cultures of all patients with cardiac disease four weeks after surgery were negative and that none of these patients showed any signs of subacute bacterial endocarditis after careful history and physical examination suggests strongly the value of chlortetracycline in preventing detectable bacteremia and thus presumably preventing subacute bacterial endocarditis following oral surgery and most likely surgery in any contaminated area of patients with cardiac disease.[7] Chlortetracycline, therefore, in our opinion, is an effective drug for prophylactic treatment of patients with cardiac disease prior to oral surgery, as it can be given orally, has a relatively low toxicity, and does not lead to the development of drug-resistant organisms.

Mrs. Lotte Hartwich and the Misses Mary Sullivan, Phyllis Landano, and Isabel Shepard gave assistance in the clinic and laboratory.

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HYPERGAMMAGLOBULINEMIA IN PULMONARY TUBERCULOSIS

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THE LEVEL of gamma globulin in the serum is elevated in chronic inflammatory conditions even though the disease may be localized in a single organ. This has been related to the antibody response on the part of the host. However, this excess gamma globulin is by no means all antibody but is rather an "inert reaction globulin," [1] which is only one expression of a generalized nonspecific reaction involving many organs. The availability of newer and simpler biochemical methods and biopsy techniques makes it possible to try to correlate structural and functional alterations in the living patient. This study represents the attempt to find the remote structural changes in pulmonary tuberculosis which are related to the level of the gamma globulin in the serum. In addition, the significance of serum gamma globulin elevation in estimating the extent of the nonspecific host reaction in the liver is evaluated.

MATERIAL AND METHODS

A group of 23 patients with active far-advanced pulmonary tuberculosis with no evidence of miliary spread, amyloidosis, or involvement of distant organs was selected. They had all been hospitalized over two months and had been under treatment with streptomycin, *p*-aminosalicylic acid, isoniazid, or some combination thereof. The patients were on a well-balanced diet of at least 2,600 calories and were all fairly stable as far as the disease process was concerned. Three patients had controlled diabetes mellitus, which did not influence this present study as far as could be determined.

The serum gamma globulin was determined turbidimetrically according to the method of de la Huerga and Popper.[2] Serum mucoproteins were determined according to Winzler and associ-

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From the Oak Forest Tuberculosis Hospital, Oak Forest, Ill., and the Hektoen Institute for Medical Research of the Cook County Hospital.

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ates,[3] and serum polysaccharides were estimated by the diphenylamine reaction.[4] The sedimentation rate was determined according to Wintrobe. Sternal bone marrow was obtained by aspiration and stained with Wright's stain. A needle biopsy specimen of the liver was obtained with a Vim-Silverman needle. The core was fixed in Zenker-formalin and stained with hematoxylin and eosin. In six patients with cervical lymphadenopathy a lymph node biopsy was performed.

Without the condition of the patient being previously known, the liver tissue was graded 0 to 3+ as to the degree of liver cell damage, focal necrosis, Kupffer cell mobilization, portal triad infiltration, and regeneration.[5] The individual degrees of change were added together in each case to obtain the total degree of hepatic alteration. Findings such as intralobular and periportal cholangiolar proliferation, wear and tear pigment, and glycogen nuclei were not included in estimating this total degree of alteration.

The level of the gamma globulin in the serum was correlated with the following findings, using Pearson's product moment method[6]: the total degree of hepatic alteration, the number of plasma cells and monocytes in the bone marrow, the myeloiderythroid ratio, and the serum mucoprotein and polysaccharides. Correlation coefficients which showed a t value above 2.5 when tested by the null hypothesis were considered statistically significant.

TABLE 1.—*Mean, Standard Deviation, and Percentage of Abnormal Findings in Blood in Twenty-Three Cases of Pulmonary Tuberculosis*

	Mean	S. D.	Abnormal Findings, %
Serum gamma globulin, gm./100 ml.	1.90	0.68	74
Serum mucoproteins, mg./100 ml.	4.98	2.10	61
Serum polysaccharides, optical density	0.31	0.09	43
Erythrocyte sedimentation rate, mm./hr.	30.1	9.60	91

TABLE 2.—*Means and Standard Deviations of Bone Marrow Findings in Twenty-One Cases of Pulmonary Tuberculosis*

	Mean	S. D.
Plasma cells, %	1.65	1.06
Monocytes, %	3.14	1.81
Myeloid:erythroid ratio, %	4.39	1.52

RESULTS

The serum gamma globulin levels were elevated above 1.25 gm. per 100 ml. in three-fourths of the patients (Table 1). The highest level was 6.25 per 100 ml. The mucoproteins and polysaccharides were less frequently abnormal.

The mean bone marrow findings all were within the normal range (Table 2). Only three patients (14%) had more than 3% plasma cells (3.1, 6.2 and 6.3%). The lymph nodes uniformly showed the same changes; namely, nonspecific hyper-

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plasia of both lymphoid and reticular elements, with somewhat distorted architecture. There was no increase in the number of plasma cells. These changes bore no relation to any other histologic or biochemical findings.

The most common histologic finding in the liver, present in over 90% of the biopsy specimens, was an increase in the size and number of Kupffer cells (Table 3). Focal necrosis, liver degeneration, and infiltration of the portal triads were present in about two-thirds of the cases. Other alterations, such as regeneration, cholangiolar proliferation, and the presence of wear and tear pigment, were less frequently found. Glycogen nuclei were present in the liver cells in the three patients with diabetes mellitus.

In spite of the rather crude way in which the total degree of hepatic alteration was estimated, it showed a statistically significant correlation with the gamma

TABLE 3.—*Incidence of Hepatic Abnormalities Found in Liver Biopsies in Twenty-Three Cases of Pulmonary Tuberculosis*

Abnormality	Cases, %	Abnormality	Cases, %
Liver cell degeneration	65	Regeneration	43
Focal necrosis	70	Wear and tear pigment	39
Kupffer cell mobilization	91	Cholangiolar proliferation	26
Portal triad infiltration	61	Glycogen nuclei	13

TABLE 4.—*Correlation Coefficients Between Levels of Serum Gamma Globulin and Hepatic Alterations, Bone Marrow Findings, and Certain Blood Findings*

	Degree of Hepatic Alteration	Bone Marrow Findings			Findings in Blood		
		Plasma Cells	Monocytes	M-E* Ratio	Sed. Rate*	Mucoproteins	Polysaccharides
Gamma globulin	0.61†	0.58†	—0.37	—0.27	0.25	0.30	0.65

* M-E = myeloid:erythroid; Sed. rate = sedimentation rate.
† Statistically significant.

globulin level (Table 4). When correlation coefficients were calculated separately for the individual histologic features indicating parenchymal changes (liver cell degeneration, focal necrosis) and mesenchymal reaction (Kupffer cell mobilization, portal triad infiltration), no significant correlation was found. The only other factor which showed a statistically significant correlation with the serum gamma globulin level was the number of plasma cells in the bone marrow.

COMMENT

Previous studies have shown that plasmacytosis is common in chronic inflammatory conditions [7] and hypersensitivity states.[8] This has also been associated with

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increased serum globulin levels [9] and increased antibody formulation.[10] The present findings are in keeping with the possibility that part of the hypergammaglobulinemia in pulmonary tuberculosis is related to the number of plasma cells in the bone marrow, although the increase in the individual case is not impressive.

The liver has also been associated with antibody formation.[11] Increased antibody formation has been demonstrated in both acute [12] and chronic [13] hepatic disease, and it has been suggested that the hypergammaglobulinemia of liver disease is due to increased production by the hepatic mesenchyme in response to parenchymal degeneration.[14] Recent in vitro tracer studies point to the hepatic parenchymal cell as playing a more direct role in antibody formation.[15] The results of the present study would agree with the hypothesis that the liver is a source of some of the increased serum gamma globulin. In view of the statistical findings, it is possible that both parenchymal and mesenchymal elements participate.

The level of the gamma globulin in the serum is therefore a fairly reliable index of the severity of the nonspecific reaction in the liver to a chronic inflammatory disease, although it is not necessarily a measure of the amount of circulating antibody. The serum mucoproteins and polysaccharides, which are also frequently altered in tuberculosis and probably indicate the degree of local tissue destruction,[16] are not related to this nonspecific host reaction. The erythrocyte sedimentation rate, which is an indication of the activity of the disease, is also not related to this reaction.

SUMMARY AND CONCLUSIONS

Serum levels of gamma globulin, mucoproteins, and polysaccharides in 23 patients with far-advanced active pulmonary tuberculosis were correlated with changes found in liver and lymph node biopsy specimens and sternal marrow findings. Statistically significant correlations were found between the level of the serum gamma globulin and both the total degree of hepatic alteration and the number of plasma cells in the bone marrow. The level of serum gamma globulin is an index of the severity of the nonspecific host reaction seen in the liver.

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PERIODIC DISEASE

Observations on Old Cases and Report of New Cases and of Therapeutic Trials

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IN PREVIOUS publications the name periodic disease was proposed to cover an assortment of disorders of unknown cause which have in common regular short episodes of disease recurring over many years without affecting the general health.[1] They were named according to their outstanding clinical feature, respectively, as periodic fever, periodic abdominalgia, periodic arthralgia, and periodic neutropenia. Certain cases of anaphylactoid (Schönlein-Henoch) purpura and of angioneurotic (Quincke's) edema were included in the scheme with the new names of periodic purpura and periodic edema, but the place of periodic paralysis, the cyclic vomiting of children, and others was uncertain. After a review of the subject was published,[2] new cases of the kinds already described, some of them with unusual features, and examples of other recurrent disorders came to my attention. They were gathered by correspondence with physicians, from published reports in journals, from the Queries and Minor Notes column of *The Journal of the American Medical Association*, and by letters and visits from victims of the disorders who read comment on the subject in a popular periodical.[3] A description of some of these new cases, continued observations on a few patients previously described, and a report on therapeutic attempts form the basis of the present essay. For convenience in reference, previously reported cases are designated by the numbers originally used.

PREVIOUSLY REPORTED CASES

CASE 1.—Mrs. N. W., aged 54, has had bouts of chills, fever, thoracic and abdominal pains, pains in the extremities, headache, puffiness, nausea, and vomiting since 1936. In recent years, the abdominal pain disappeared, leaving arthralgia and myalgia as the chief annoyance. Febrile episodes with arthralgia come regularly every 17 to 21 days, as shown in Chart 1. The patient is steadily employed but spends an uncomfortable day or two in bed during most episodes. She has endured about 300 episodes since they began, 17 years ago.

As an experimental therapeutic procedure, conducted by Dr. John N. Lindquist, cortisone (Cortone)[4] was given in daily doses of 100 mg. from Oct. 11 to 29, 1951, when the dose was

From American University, Beirut, Lebanon; Dr. Reimann is Visiting Professor of Medicine.

1. (*a*) Reimann, H. A.: Periodic Disease: A Probable Syndrome Including Periodic Fever, Benign Paroxysmal Peritonitis, Cyclic Neutropenia and Intermittent Arthralgia, J. A. M. A. **136**:239-244 (Jan. 24) 1948; (*b*) Periodic Disease: Periodic Fever, Periodic Abdominalgia, Cyclic Neutropenia, Intermittent Arthralgia, Angioneurotic Edema, Anaphylactoid Purpura and Periodic Paralysis, ibid. **141**:175-183 (Sept. 17) 1949.

2. Reimann, H. A.: Periodic Disease, Medicine **30**:219-245 (Sept.) 1951.

3. Fever Every Wednesday? Time **58**:77 (Aug. 13) 1951.

4. Cortone was kindly supplied by Dr. J. M. Carlisle of Merck & Company, Inc.

reduced to 50 mg. and given until Nov. 20, over 40 days in all. There was an elevation of eosinophiles to 26% before injection of 100 mg. of cortisone and 4 hours later to 30%. Before therapy the glucose-tolerance test, at hourly intervals, read 92, 114, 120, and 110 mg. The glucose in the blood at intervals during therapy measured 83, 96, and 75 mg. per 100 cc.; the plasma chlorides, 500 mg. The usual changes in the quantitative excretion of hormones in the urine occurred during therapy.

As shown in Chart 2, a typical episode expected about Oct. 20 is not evident; fever did not occur, but there was pain in the left shoulder and swelling of the neck. Fourteen days later, the temperature rose briefly to 100.2 F. with headache, but the next episode occurred in its usual form. Thereafter, even though therapy had been discontinued, only one typical bout occurred in three months. Short mild febrile periods appear on schedule in the temperature tracing, each one greater in intensity and duration, until the characteristic routine is reestablished in March. Apparently a delayed effect of cortisone suppressed the signs and symptoms of several episodes but had no influence on their rhythm or subsequent course. The patient refused further hormonal therapy and preferred the discomfort of the episodes to the mental depression caused by cortisone.

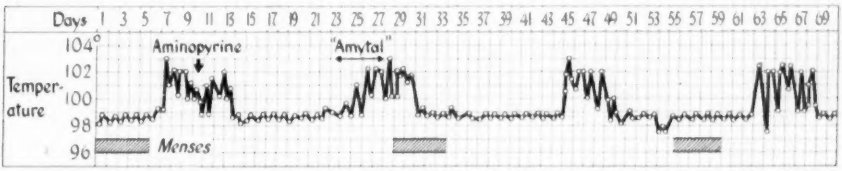

Chart 1 (Case 1).—Reproduction of a portion of a chart published in 1948 to show the usual course of events. Episodes still come at 19- to 21-day intervals and last four to six days.

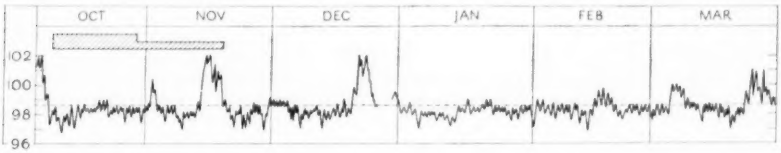

Chart 2 (Case 1).—The course during and after therapy with cortisone. During therapy, indicated by the hatched bar, an episode expected in October consisted only of fever (99 F.) on three days. In the next episode temperature was 100.2 F. for one day, but 19 days later an episode occurred in its usual form. A characteristic episode is shown in December, after therapy was stopped. Thereafter, no significant fever is shown until February, and the succeeding episodes increased in intensity until the usual rhythm, shown in Chart 1, was resumed.

Success was reported by Willis in treatment of a patient with a similar disorder with paraaminobenzoic acid.[5]

On the second day of an episode in November, 1951, Mrs. N. W. received 3 gm. of sodium and potassium paraaminobenzoate in 10% solution, three times a day, and for several days thereafter. There was no effect on the episode or on the succeeding ones. The patient declined further therapy because of the nausea it caused.

Case 2.—S. L., now aged 32, has had periodic abdominalgia at weekly intervals for 15 years. For several months in 1951, and occasionally since then, pain and stiffness of the right elbow accompanied the episodes of abdominalgia. He received 60 mg. of corticotropin subcutaneously for six days. Because of unpleasant symptoms the dose was reduced to 20 mg. for two days

5. Willis, W. H.: Treatment of Benign Paroxysmal Peritonitis with Para-Aminobenzoic Acid, J. A. M. A. **147**:654-656 (Oct. 13) 1951.

and to 10 mg. for five days. During therapy over 13 days, two characteristic episodes of pain in the chest and right side of the abdomen, myalgia, fever, nausea, and headache occurred. Subsequent bouts were uninfluenced.

In September, 1951, therapy with paraaminobenzoic acid was conducted by Dr. Henry Walter, of Lancaster, Pa., in the manner recommended by Willis. It had no effect on the severity or periodicity of the episodes.

Case 9.—Mrs. R. C. has had episodes of fever at short intervals since 1945. According to information received in 1950, bouts came at 8- and 9-day and sometimes at 14-day intervals. The temperature was lower and the fever shorter in duration than previously. After a severe emotional disturbance the cycle, for a time, reverted to four-day periods, as in 1946, with temperatures of 102 or 103 F. In a letter received in 1952, the patient wrote that she had been free of episodes for nine months, but they resumed after another emotional disturbance. They are mild, and the temperature has seldom exceeded 100 F. except in three episodes during the year, when it reached 102 F. Episodes still come at intervals of about seven days.

Case 10.—Mrs. O. T. O., now aged 44, was studied on many occasions at the Presbyterian Hospital in New York City, for episodes of fever and abdominal pains which have recurred for 42 years. In recent years episodes of abdominalgia are sometimes replaced by episodes of arthralgia, as in Case 1. Mastectomy for carcinoma was performed and a pregnancy was terminated artificially in 1950. The patient's physician treated her empirically with para-aminosalicyclic acid with no result. Methantheline (Banthine) at times seems to lessen the severity of the discomfort.

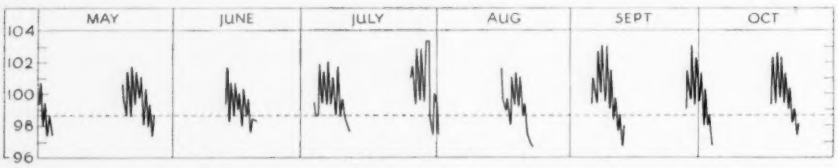

Chart 3 (Case 23).—A portion of the patient's diary transposed to chart form. Episodes come at about 21-day intervals. The patient recorded his temperature after he noted anorexia, malaise, and cold extremities, which precede fever in each episode. The temperature was normal in the free intervals.

Mr. G., a patient of Dr. H. L. Wolf, of Texas (not referred to by number [2]), who has had periodic abdominalgia for 42 years, was given cortisone orally. While he was under therapy for six days, a typical episode occurred, and subsequent ones recurred as before.

REPORT OF NEW CASES

Periodic Fever

Case 23.—Mr. W. B., aged 68, had hematemesis from hepatic cirrhosis in 1948 and viral pneumonia in March, 1949. In April, 1949, recurrent attacks of chills and fever began, and of his own accord, he kept a written record of the temperature. Transposition to chart form of part of his record, in 1950, is illustrated in Chart 3. One day before each episode of fever there are coldness of the hands and feet, anorexia, and malaise. Chills and sweating, noted when the trouble first began, no longer occur. The patient recorded his temperature after the symptoms of each episode began. It was normal between the episodes. At first, episodes came at 24-day intervals; lately, they have occurred every 21 days. The patient plans on one week of discomfort and two weeks of unhampered work. Aureomycin was taken during many episodes, without influence on the fever.

Episodes in this patient began later in life than in most others. They describe the clearest example of periodic fever.

PERIODIC ABDOMINALGIA

CASE 24.—Z. T., aged 50, an Armenian residing in Boston, began to have attacks of fever at the age of 4 years, which as the years went by came every two weeks and were characterized by a temperature of 103 F. and thoracic pain in one or both sides of the chest. After the age of 23, severe pain in the abdomen appeared in addition, accompanied by violent diarrhea. The attacks are ushered in by dryness of the mouth and swelling of the gums. The patient has persistent edema of the ankles. Visceral pain and generalized myalgia in the episodes are severe. In 1933, 1936, and 1948, periods from six to nine months elapsed without any episodes. Relief sometimes is afforded by phenobarbital and whisky. His tonsils, appendix, gall bladder, and a rib were removed in futile attempts at therapy. Sympathectomy and splenectomy were proposed but not accepted.

This case with coincident stethalgia, myalgia, and edema and Cases 1, 2, 10, and 25 with arthralgia demand the use of less restrictive terms than periodic abdominalgia or paroxysmal peritonitis to designate them.

CASE 25.—Mrs. V. P., aged 29, of Armenian descent, at the age of 5 years had attacks of pain and swelling in her joints about every two or three weeks, supposedly rheumatic in origin. At the age of 6 years abdominal pain and fever led to appendectomy. Abdominalgia recurred about twice a year until the age of 11 years, when operation for suspected intestinal obstruction was done. Since that time, the patient has had repeated bouts of severe abdominal pain with nausea, vomiting, chills, fever, and anorexia lasting about five days. Narcotics were given for pain. In 1944, at the age of 21, pain, swelling, redness, and heat appeared in the left sterno-

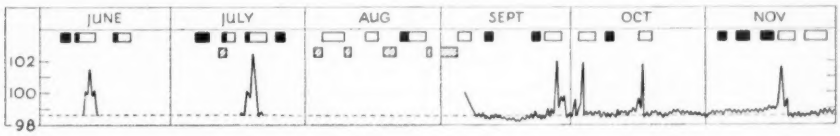

Chart 4 (Case 27).—Representative portion in chart form of the patient's diary kept from July, 1948, to December, 1950. The open blocks represent periods of severe abdominalgia; the black blocks indicate periods of mild abdominal pain; the cross hatched ones, periods of arthralgia. Each occurs at irregular intervals in no relation to the others. Fever occurs only during periods of severe abdominalgia.

clavicular joint for two months, followed by pain in the right wrist and knees. The patient then was free of arthralgia for a year, when it returned and recurred irregularly in a knee after 1947. After marriage, in 1947, the patient gained 61 lb. (27.7 kg.) in weight. Episodes came three to four times a year, but since 1948, after the age of 25, their frequency increased. The patient's case was studied by many physicians at four hospitals.

The patient came under my observation in November, 1950. No significant abnormalities except obesity were found. There were no murmurs or other evidence of rheumatic fever. On several occasions the patient complained of severe pain and tenderness in the left wrist and abdomen, and fleeting urticaria was observed. A psychiatrist regarded the patient as having a dependent personality or a psychopathic disorder to account for obesity, urticaria, and her other troubles. A lesion in the hypothalamus or a parahypothalamic tumor was suggested as a cause. The blood cell count was normal, and the sedimentation rate was 20 to 30 mm. in one hour. Leucocytosis did not accompany the episodes of pain. The basal metabolic rate was —6%. The quantitative estrogens in the urine measured less than 12 mg.; the gonadotropins, less than 6 mg., and the 17-ketosteroids, 2.8 mg. An electrocardiogram was normal.

The patient on her own accord had kept a diary of her troubles from June, 1948, to December, 1950. Episodes of abdominal pain were recorded at irregular intervals of 10 to 32 days, with an average interval of 17 days. In 1949, abdominalgia occurred oftener but irregularly, averaging every 12 days. Eight episodes of arthralgia were spaced at 13- to 144-day intervals in no relation to the abdominal pain. In 1950, abdominal episodes came at periods

averaging 16 days, but numerous minor episodes increased the frequency. Six episodes of arthralgia and many of abdominalgia are shown graphically in an excerpt of the long record (Chart 4). Fever (102 F.) usually accompanied severe abdominalgia.

As stated, narcotics were given for pain. Obviously, in periodic disease lasting for years, the hazard of habituation forbids their use.

CASE 26.—Dr. Marvin Pizer, of Los Angeles, has a Jewish patient, aged 32, who has had abdominal pain at intervals of 7 to 14 days for five years. The pains come in spells of six weeks to three months. Of six siblings, one has migraine and a brother has a disorder almost exactly like that of the patient.

Dr. Pizer also informed me of Jewish adult male triplets, each of whom has periodic abdominalgia. These are further examples of the familial and ethnologic tendency to periodic disease.

CASE 27 (Report supplied by Dr. Gerald B. Phillips, Boston).—J. L., aged 32, entered the Presbyterian Hospital in New York in 1949 complaining of stomach pains occurring for 17 years. Appendectomy was performed in 1932. Six months later recurrent episodes began. The patient was troubled every three to four months by severe colic lasting 10 to 20 minutes several times a day over 3 to 10 days. Shaking chills, temperatures at times as high as 105.6 F., and leucocytosis accompany the episodes. The pain occurs anywhere in the abdomen and remains in the same place, most frequently in the right lower quadrant. During the episodes there is a "lumpy thickening" in the groin on the same side as the abdominal pain. Exploratory laparotomy in 1938 revealed adhesions.

The patient was a well-developed healthy man. The only significant findings during an episode were moderate spasm of the abdominal wall, slight tenderness in the left lower quadrant, and a thick tender left spermatic cord, about 1 cm. in diameter. The swelling extended to the upper pole of the left testicle and gradually subsided. All laboratory tests and studies gave negative results except for leucocytosis, with a cell count of 18,000. Temperatures did not exceed 100.4 F.

During a second study period in the hospital, urologists added no information. A diagnosis of recurrent thrombophlebitis of the spermatic vessels (recurrent funiculitis) was made.

This case may be classified as one of periodic abdominalgia with involvement of the spermatic cord.

CASE 28 (Information supplied by Dr. H. A. Lawson, Providence, R. I.).—Mr. A. S., an Armenian, aged 39, has had recurrent severe abdominal pain lasting one or two days for 34 years. The interval gradually shortened from three or four times a year to 10 to 14 days in winter and 14 to 21 days in summer. A free period of three months once occurred. Appendectomy and cholecystectomy were performed without affecting the disorder. The patient entered the Navy in 1943 but was kept in hospitals for study most of the time.

While he was in a Providence hospital for study, an episode began with malaise and anorexia. Fever (101 or 102 F.) then occurred, accompanied by severe pain in the abdomen, which subsided in about 24 hours. Physical examination revealed nothing abnormal aside from the operative scar, and results of all laboratory studies were within normal limits.

In a letter, Prof. A. Querido, of Leiden, informs me of a patient of his who had periodic abdominalgia for 19 years, in whom three episodes were suppressed by cortisone given the day before a predicted episode and for three days afterward. Subsequent treatment was ineffective.

PERIODIC ARTHRALGIA

CASE 29 (Information supplied by Dr. H. A. Lawson, Providence, R. I.).—Mr. H. M., aged 40, began to have recurrent episodes of fever and arthralgia in 1949, at three- to four-month intervals. The symptoms are preceded by sore throat, chills, and fever for which he regularly takes a sulfonamide drug and aureomycin. Two days later there are pains in the joints

generally and swelling and redness of the wrists. The temperature rises at times to 102 F. A few hours later, urticaria of the buttocks, arms, and legs and swelling of the lids occur. Arthralgia subsides in three to four days. Physical examination, aside from a moderately inflamed pharynx, was unrevealing, and laboratory studies gave normal results. There was no eosinophilia. The sedimentation rate was 41 mm. in an hour during an episode and 3 mm. in a free period.

This case is an unusual example of periodic arthralgia; ordinarily fever does not occur.

CASE 30.—Information was requested from the editor of a medical journal [6] as follows:

"I have a patient for whom a diagnosis of dengue fever was made in service in World War II. He still complains of fever, generalized aches, and arm tenderness at recurring intervals of approximately every three months. Can you inform me of proper treatment for this condition at this stage?"

The answer to the query advised consideration of brucellosis, tuberculosis, Hodgkin's disease, canicola fever, and neoplasm. The possibility of periodic arthralgia was not mentioned. Meager additional information which I obtained by correspondence revealed the patient's age as 36; the episodes began in 1944 and last three to five days.

CASE 31.—Mr. V. S., aged 47, resident in France, has noted swelling and pain in his ankles, knees, and hips, usually of the left side, either singly or in combination, lasting 24 to 48 hours every 11 days, for over 40 years. No treatment has given relief. During a period of semi-starvation in a concentration camp in 1943, the episodes came as usual. The patient's sister and two cousins have similar disorders, but his three children thus far are not affected.

CASE 32.—Mrs. F. T., aged 64, resident in Puerto Rico, has had pain in the joints of her legs at irregular intervals for many years. She is not incapacitated by them. Repeated studies failed to reveal the cause, and no treatment is helpful. In a registered period over two months, the intervals between three episodes were 19 and 30 days. Pain lasted three to five days.

Victims with mild forms of periodic arthralgia, as in this case, seldom come to medical attention.

PERIODIC NEUTROPENIA

Cobet and Schilling report the case of a woman observed over six years.[7] Neutropenia and monocytosis recurred every 21 days, accompanied by oral ulcers and abscesses elsewhere. Splenectomy relieved the symptoms but left the neutropenic cycles unchanged. In Sandella's case a woman had an ischiorectal abscess at the age of 64.[8] Leucopenia with 4% neutrophilic cells was noted. The leucocytes returned to normal for about three months, when ulcerative stomatitis, cervical adenitis, pustular lesions on the scalp and hands, and absolute neutropenia lasting 10 days were noted. Then, after another period of good health for two months, regular 21-day cycles of chill, fever, stomatitis, and neutropenia began. Splenectomy was performed after the eighth episode. Thereafter, cycles came at 21-day intervals for several months but lengthened to about 60 days, and, as in other reported cases, after splenectomy the symptoms lessened or disappeared. Although biopsy of the spleen and liver had revealed no evidence of it at operation, lymphosarcoma caused death 16 months later. Moncrieff reported a case of

6. Recurring Fever, Queries and Minor Notes, J. A. M. A. **148**:326 (Jan. 26) 1952.

7. Cobet, R., and Schilling, V.: Periodische-rezidivierende Neutropenie mit Monocytose: Das Krankheitsbild der periodischen Neutropenie oder cyclischen Agranulocytose, Folia haemat. **70**:286-303, 1951.

8. Sandella, J. F.: Cyclic Acute Agranulocytosis: Report of Case with Improvement after Splenectomy, Ann. Int. Med. **35**:1365-1371 (Dec.) 1951.

recurrent neutropenia in a child 2 years of age.[9] In another instance, a man of 78 had had periodic neutropenia at three-week intervals for a year.[10] Clinical improvement followed splenectomy and therapy with corticotropin.

MISCELLANEOUS PERIODIC DISORDERS

Dermal Manifestations

Case 33.—Professor H. C., aged 70, injured the skin of his right leg in December, 1948. The lesion failed to heal until June, 1949. In November, 1949, two "sores" appeared on the lower left leg; they gradually multiplied and eventually involved the greater part of both limbs. A diagnosis of nummular eczema was made. The patient noticed that the number of spots increased and decreased in cycles. A cycle begins abruptly with itching and, over several days, an increase in the number of lesions to 100, occasionally to over 200. Most of them disappear after a few days, but 10 or more are constantly present between episodes. The lesions are red macules or papules 1 mm. in diameter, surrounded by faint erythema 0.5 cm. in diameter, symmetrically distributed over both legs.

Because of the periodicity of the eruption, the patient kept a diary noting the date on which itching began and the number of lesions daily. The number was estimated by counting those on one thigh and multiplying by 4. To his surprise, the episodes came at fairly regular intervals. According to his record, beginning in December, 1950, they appeared at seven-day intervals, "every Friday" for six weeks, but slight irregularities soon advanced the day on which they appeared. Itching was recorded at intervals of 14, 7, 7, 14, 20, 8, 12, 31 days and so on, as shown in Chart 5. An increase in the number of lesions regularly followed itching and

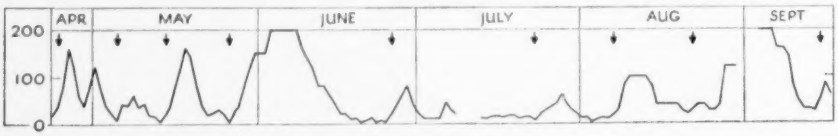

Chart 5 (Case 35).—Representative portion in chart form of the patient's diary kept from December, 1950, to January, 1952. The onset of itching is indicated by the arrows, and the estimated number of lesions, by the line. The episodes are more widely spaced in the summer months, the intervals averaging 20.4 days.

at times took place when no itching was recorded, or the lesions persisted in large numbers for two or three weeks, probably obscuring the weekly onset of itching. The patient's oral temperature, measured before rising, over a two-month period, ranged between 96.8 and 97.8 F. When an episode began and as the dermal lesions increased in number, the temperature regularly fell from 0.4 to 0.8 degree (F.). The average length of a cycle, as calculated for 11 periods, was 7.1 days. According to word received from the patient, in August, 1952, the lesions appear in smaller numbers and on many days none is present.

G. E., a boy aged 13 (described previously as Case 16[1b]), has had 80 episodes of severe disease since the age of 2. They come at intervals of six to eight weeks in winter and two to four months in summer; each lasts 7 to 10 days. The onset is with sore throat, fever, stupor, muscular stiffness, and enlarged cervical lymph nodes. A neurologic disturbance and a confluent, papular, multiform, erythematous or urticarial eruption which comes in crops appears. Between episodes, the patient is in good health and is normally developed for his age. Studies at many hospitals failed to reveal significant abnormalities.

Case 34 (Information submitted by Dr. A. S. Hartwell, of Honolulu, H. T.).—A. T., aged 30, of Japanese descent, first noted recurrent painful red areas on his hands and feet at the age

9. Moncrieff, A.: Recurrent Neutropenia, Arch. Dis. Childhood **26**:438-440 (Oct.) 1951.

10. Monto, R. W., and others: Periodic Neutropenia: Treated by Adrenocorticotrophic Hormone and Splenectomy: Report of a Case, New England J. Med. **246**:893-896 (June 5) 1952.

of 12. A temperature of 99 F. accompanies the eruption, which lasts two to three days and disappears. At the time of examination, there was a slightly tender macule 1 by 2 cm. in diameter on the left heel. No abnormalities were noted in routine laboratory studies.

Case 35.—A 30-year-old patient has had a recurrent vesicular eruption of his penis over seven years.[11] Lesions appear on the average of every 14 days and last about the same length of time. When one crop is nearly gone another begins. A diagnosis of herpes progenitalis was made, but no treatment has affected the disorder.

Case 36.—A woman, aged 25, noted the occurrence of scattered purpuric macules on the lower part of the legs, ankles, and feet at intervals of several days for a year, sometimes accompanied by pain in the ankles and pain in the discolored areas.[12] A recurrent tender mass in the left lower part of the abdomen led to surgical operation, but no abnormality was found. All laboratory studies gave negative results, except that on one occasion there was an eosinophile count of 12%.

This case perhaps may be classified as one of periodic purpura (Schönlein-Henoch syndrome, anaphylactoid purpura).

Case 37.—A youth, aged 18, had recurrent episodes of generalized edema and urticaria at monthly intervals.[13] The episodes began abruptly two years ago after one occasion when the patient felt pain in his neck, left shoulder, and thorax. Numerous skin tests revealed no sensitivity to the proteins used. Attempts at desensitization to histamine gave no relief. Biopsy of a muscle revealed no abnormality. During the episodes the leucocytes numbered 13,000 to 23,000, of which 75% were eosinophiles, and the sedimentation rate was 62 mm. in one hour. In differential diagnosis, trichinosis, periarteritis, and eosinophilic leukemia were considered. It would seem that periodic edema (angioneurotic, or Quincke's, edema) may be the correct diagnosis. When the patient was last heard from, in December, 1951, the condition was unchanged.

Dermal lesions are recorded in Case 16 [1b] and in cases of neutropenia and are present as urticaria in cases of periodic abdominalgia.

Periodic Neurologic and Respiratory Tract Disorders

Case 38 (History supplied by Dr. R. W. Hillman, of Brooklyn).—A nurse, aged 24, was afflicted with "fainting spells and rolling of the eyes" every two months for a year at the age of 5. At the age of 18, in 1946, she began to have recurrent episodes of acute nasopharyngitis which lasted six days. She was admitted to the hospital for study on 15 occasions up to November, 1951. The episodes came at variable intervals of one to eight months but on five occasions at intervals of two months. However, the patient had many mild episodes of which no record was kept.

In an episode in May, 1947, there were sore throat, headache, drowsiness, chill, fever (temperature 105 F.), and nuchal rigidity and Kernig's sign were demonstrable. There were 88 cells in the cerebrospinal fluid, which contained 50 mg. of protein and 75 mg. of sugar. In January, a similar episode occurred, accompanied in addition by nausea and vomiting. The pressure of the spinal fluid was 300 mm. It contained 14,000 cells, 125 mg. of protein, and 65 mg. of sugar. Similar episodes followed at two-month intervals in August and October, each lasting two or three days, but the cells in the spinal fluid then numbered 85 and 3, respectively. A mild bout with nasopharyngitis and low-grade fever alone was observed in November, 1947 and, after six months, in May of 1948. Two months later, in July, there was a two-day bout of

11. Recurrent Herpes of Penis, Queries and Minor Notes, J. A. M. A. **139**:1303 (April 30) 1949.

12. Purpura Rheumatica, Queries and Minor Notes, J. A. M. A. **143**:406 (May 27) 1950.

13. Recurring Edema and Urticaria, Queries and Minor Notes, J. A. M. A. **144**:886 (Nov. 4) 1950.

nasopharyngitis with diplopia, vomiting, and meningismus, with 15 cells in the spinal fluid. A similar episode was observed in October, when 220 cells were counted. There were six episodes up to November, 1951, each characterized by two- or three-day periods of nasopharyngitis, some with cough, nuchal rigidity, vomiting, and stupor, and one with a tender palpable liver. Subsequent episodes, up to August, 1952, were irregular and consisted chiefly of sore throat, cough, headache, and, occasionally, arthralgia.

On various occasions, therapy with penicillin and sulfadiazine had no effect. Aureomycin given prophylactically failed to prevent episodes. Despite the distressing symptoms, the patient otherwise is well, has gained weight, and is normal in all other respects. All routine and special laboratory tests, including serologic search for evidence of known forms of meningitis and encephalitis, were fruitless. Many consultants were unable to arrive at a diagnosis.

It is possible that the patient has a bizarre form of periodic disease. It is likely that the two-month cycle of "fainting spells" experienced in childhood was a manifestation of the same underlying cause. It is impossible to account for meningitis during many of the short episodes and equally difficult to explain why nasopharyngitis occurs. Periodic neurologic and respiratory tract symptoms and signs of similar nature were recorded also in Case 16[1b] and periodic respiratory tract disorder is noted in Cases 29, 39, and 40.

Reference has been made twice before in this paper to Case 16,[1b] that of the boy of 13 who had had many severe episodes at intervals of six to eight weeks in winter and two to four months in summer. On one observed occasion there were nasopharyngitis, cervical adenopathy, dermal eruption, and signs of meningismus; namely, positive Babinski and Kernig signs, absence of patellar reflexes, and irregular respiration for 10 days. The leucocytes numbered 18,000; temperature was 104 F. The spinal fluid was normal. The episodes, as in Cases 28, 33, and 39, came at longer intervals in summer. At first, in infancy, episodes consisted only of evidence of infection of the respiratory tract. Gradually they became severer and included fever (temperatures of 104 to 105 F.), drowsiness, stupor, polydipsia, polyuria, anorexia, diarrhea, dermal eruption, nuchal rigidity, and general muscular stiffness in various combinations in different episodes. The episodes last 7 to 10 days, and the patient is well between times except for mild spasticity, congenital cataract, and ptosis of the right lid.

In differential diagnosis encephalitis, meningitis, brain tumor, cysticercosis, craniopharyngioma, Hodgkin's disease, and Friedreich's ataxia were considered. Allergic and infectious causes were sought without success. A hypothalamic lesion was thought by the patient's physicians to account best for the disorder.

Reference also may be made to Case 38, in which nasopharyngitis was accompanied by meningitis.

Case 39.—P. P., previously referred to briefly,[2] involved a man of 21. His physician requested diagnostic aid to explain recurrent attacks of pain in the penis and perineum.[14] I obtained more detailed information by direct correspondence. The trouble began in May, 1949, but episodes were not recorded until December, 1949, after which 12 are registered up to May, coming at intervals varying from 4 to 28 days, usually 7 to 9 days. Episodes in summer came only in August and September.

Episodes begin with clogged nares, rhinorrhea, sore throat, "stiffness of the chest," chills, fever, and needle-like pains in the penis and perineum. According to information received subsequently, only two episodes occurred, one in September, 1950, and one in September, 1951, each preceded by sore throat. Between times numerous unregistered "colds" without sore throat or periodic pain occurred.

14. Pain in Penis and Perineum, Queries and Minor Notes, J. A. M. A. **144**:211 (Sept. 9) 1950.

It is possible that some instances like the one just described and a case reported by Helman [15] are similar to the so-called Behcet's syndrome. This syndrome is characterized by recurrent ulceration of the oral and genital mucosa, fever, arthralgia, and dermal lesions.[16]

Periodic Vomiting of Childhood (Cyclic Vomiting)

Cyclic attacks at intervals of two or more weeks of abdominal pain and vomiting, coryza, cough, and asthma, accompanied in some children by fever, are commonly regarded as neurotic or allergic in origin, for want of a better explanation. It is doubtful in most instances whether allergy as pertains to an antigen-antibody reaction to protein bears any relation to the disorder.[17]

The question was raised elsewhere regarding the possible relationship of certain instances of the cyclic vomiting of childhood to periodic disease.[2] At that time no cases had come to my attention in which the disorder persisted into adult life or disappeared to recur later in different form. In several cases described (Cases 10, 24, and 25) periodic abdominalgia with vomiting began in infancy or early childhood. The next case report may serve as another example of such a sequence.

Case 40.—R. P., aged 40, of Washington, D. C., since childhood had one or two attacks yearly of nausea, vomiting, and fatigue, lasting three to five days. They ceased for several years while he was at college but returned thereafter at shorter intervals, about four times a year. Appendectomy gave no relief. Between the episodes he was aware of many "abortive" bouts but cannot recall their spacing in relation to the major ones.

Episodes begin with a "rough scratchy throat" which intensifies over six to eight hours, followed by anorexia and a shaking chill, which is repeated several times during the next six hours. The temperature rises to 104 F., and the fever ends in 24 hours with drenching sweat. Severe headache, general aching, vomiting, and diarrhea last three to five days, often necessitating rest in bed. The leucocytes number 11,000 to 16,000. All other laboratory data are uninformative.

This patient's son, aged 10, has similar episodes two or three times a year, lasting two or three days, with abdominal pain in addition.

Case 41 (History supplied by Col. L. J. Geppert, of Texas).—B. R., a child of 7, had pneumonia at 9 months of age followed by several spells of vomiting and diarrhea. When she was a year old a severe episode of vomiting, diarrhea, and fever (104 F.) occurred, followed a month later by a similar episode. Thereafter, episodes occurred with predictable accuracy every Thursday. Anorexia, vomiting, diarrhea, and fever persisted with diminishing intensity during the week until Wednesday, and on Thursday the cycle would recommence. Episodes were dormant for four months but returned in May, 1946 (age 19 months), at intervals of 10 days to 3 weeks. When the patient was in a hospital for study, at the age of 22 months, she was regarded as normal, except for pallor. A predicted episode, heralded by the appearance of an ulcer on the tongue, occurred punctually, with fever (103 F.) and diarrhea. Another episode occurred three weeks later, lasting five days. A third episode began 11 days after the onset of the preceding one, and a fourth 14 days later. During an episode, the leucocytes numbered from 20,000 to 27,000; on one occasion differential cell count showed 52 neutrophile cells, 1 myelocyte, 10 small lymphocytes, 3 monocytes, and 34 atypical lymphocytes per 100

15. Helman, J.: Recurrent Non-Specific Urethritis Associated witn Respiratory Catarrh, Stomatitis, Conjunctivitis and an Erythematous Vesicular Eruption of the Legs and Forearms, South African M. J. **24**:688-690 (Aug. 19) 1950.

16. Curth, H. O.: Recurrent Genito-Oral Aphthosis and Uveitis with Hypopyon (Behcet's Syndrome), A. M. A. Arch. Derm. & Syph. **54**:179-196 (Aug.) 1946.

17. Breidahl, H. G.: Syndrome of Cyclic Attacks of Allergy in Childhood, M. J. Australia **2**:961-965 (Dec. 30) 1950.

cells. Extensive studies, made at the Johns Hopkins Hospital in 1947, when the patient was 3 years of age, revealed no significant abnormalities, but tonsillectomy was performed nevertheless. No significant hypersensitivity to proteins was discovered.

Up to April, 1949, episodes recurred at two-week intervals and lasted three to four days, but, aside from fever and cervical adenopathy, the symptoms mostly disappeared. Rhinologic examination during one episode revealed partial nasal obstruction by a pale boggy mucous membrane and enlarged cervical lymph nodes.

After 1949, the cyclic regularity of the patient's trouble was confused by "very frequent respiratory infections." She developed normally, but the sedimentation rate of erythrocytes was increased persistently. For six months she had frequent swelling of the wrist, which was thought to be due to rheumatoid arthritis. Corticotropin was used without much benefit. Palindromic rheumatism was then diagnosed, but there is reason to suggest periodic arthralgia as a better diagnosis. Apparently the symptoms and signs of cyclic vomiting were replaced by those of periodic arthralgia.

Case 42.—C. L. B., a Jewish child aged 11, of Florida, had recurrent bouts of abdominal pain, allegedly since birth. She was under constant medical attention. The episodes last one to three days with fever and increased urination. Laparotomy was refused during study in Boston. In 1942, at the age of one year, recurrent abdominalgia was observed over six weeks at the Johns Hopkins Hospital. An episode was characterized by pain and rigidity in the abdomen, tachycardia, and fever (102 F). All other studies gave negative results. No diagnosis was made. According to her present physician, episodes still recur.

Case 43.—This problem with meager data was referred to the editor of a journal for aid in diagnosis.[18] A child, aged 7, has had episodes twice or thrice weekly for three years. They begin with frontal headache and abdominal pain followed in 10 to 30 minutes by vomiting. After a short period of sleep she wakens feeling well. No significant abnormalities were discovered by physical examination or in laboratory studies. There are no obvious allergic manifestations in the child or in her family.

In reply to the query, diagnostic suggestions of gastrointestinal allergy, epilepsy, emotional disturbance, migraine, and indigestion were offered. Recommendation of skin tests and an "elimination" diet was made in spite of the futility of such procedures in most instances.

Periodic Sialorrhea

Case 44 was reported elsewhere in detail.[19] A woman, aged 44, began to have periodic episodes of excessive salivation in 1949, first at monthly, then at approximately weekly intervals. At times, over 1,000 cc. of saliva was collected in containers in a 24- to 36-hour period. Otherwise the flow was normal. Both submaxillary salivary glands are constantly enlarged, but the swelling increases and becomes visible during the episodes. Slight fever preceded or accompanied most of the observed episodes together with a sense of irritation of the conjunctivas and fullness of the throat. There was constant eosinophilia from 30 to 44%.

The disorder probably is related to the ones described as recurrent parotitis, of which numerous reports are on record.[20] As a probable link with other periodic disorders, sialorrhea occurred with episodes of abdominalgia in Janeway's patient and with episodes of neutropenia in Rolland's patient, as cited elsewhere.[1a]

French observers reported 14 cases of periodic disease, in 7 of which there were recurrent renal disorders.[21]

18. Headache, Stomachache and Emesis, Queries and Minor Notes, J. A. M. A. **147**:206 (Sept. 8) 1951.

19. Reimann, H. A., and Lindquist, J. N.: Periodic Sialorrhea: Report of a Case, J. A. M. A. **149**:1465-1467 (Aug. 16) 1952.

20. Bass, H. E., and Mendlowitz, M.: Relationship of Chronic Recurrent Sialadenitis to the Alarm Reaction, Ann. Otol. Rhin. & Laryng. **58**:868-872 (Sept.) 1949.

21. Mamou, H., and Catton, R.: La maladie périodique: sur 14 cas personnels dont 8 compliqués de néphropathies, Semaine hôp. Paris **28**:1062-1070 (April 2) 1952.

COMMENT

The present paper deals with further observations and study of previously reported cases and with continued attempts to collect, classify, and catalogue new examples of periodic disorders in the hope of deriving some etiologic clue and of devising preventive or therapeutic measures. So far none has been discovered.

As before, many of the new patients had visited a succession of physicians. They had undergone extensive investigation and various surgical operations or other forms of expensive therapy without getting either a diagnosis or relief. Several patients were aware of the periodic nature of their troubles and kept diaries, which are helpful in diagnosis. The importance of the problem is suggested by the frequency with which physicians appeal for diagnostic aid for their patients' disorders in the Queries and Minor Notes column of *The Journal of the American Medical Association*. In reply they usually receive the customary advice to consider brucellosis, lymphoma, neoplasm, rheumatic fever, tuberculosis, malaria, sarcoidosis, epilepsy, allergy, neurosis, and focal infection as diagnostic possibilities. Needless to say, in the early stage of periodic disease or when its victims are first seen these diseases or any others must be ruled out. But after a disorder of the kinds described persists for years in regularly recurrent uniform episodes, separated by spans of well-being, and does not affect the general health, a diagnosis of periodic disease is in order.

As predicted in an earlier publication, further search for periodic disorders revealed a number of bizarre examples. These, together with ones previously described, exhibit a surprising array. Periodic disturbances involve the abdomen, chest, joints, muscles, meninges, skin, mucous membrane, marrow, salivary glands, spermatic cord, rhinopharynx, body temperature, blood platelets, and permeability of vessels. Obviously the diversity of these benign conditions engages the attention of different medical specialists. Their frequent onset in infancy is of importance to pediatricians.[22] Surgeons are puzzled by the symptoms of periodic abdominalgia; hematologists encounter periodic neutropenia,[23] and purpura, urticaria, and cutaneous lesions interest dermatologists. Neurologists are consulted for concomitant nervous manifestations, and psychiatrists are concerned because the disorders are apt to be regarded as neuroses or the patients as malingerers. Vasomotor disturbances, especially, intrigue allergists.

Evidence continues to point to some underlying occult rhythm as the common cause of various periodic disorders. The rhythm in certain persons provokes a synchronous resurgence of a set of signs and symptoms characteristic of the respective variety of periodic disease. At present, there is no better explanation. Continued study failed to incriminate infectious or endocrinal disturbances as the cause. Allergy most frequently is suspected, yet neurovascular changes and eosinophilia are incited by other factors as well,[24] and apparently by whatever causes periodic disease.

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22. Wyllie, W. G., and Schlesinger, B.: The Periodic Group of Disorders in Childhood, Brit. J. Child. Dis. **30**:1-21 (Jan.-March) 1933.

23. Reimann, H. A., and de Berardinis, C. T.: Periodic (Cyclic) Neutropenia, an Entity: A Collection of 16 Cases, Blood **4**:1109-1116 (Oct.) 1949.

24. Lecomte, J.: Eosinophile et diagnostic des affections allergiques, Rev. méd. Liège **6**:682-685 (Oct. 15) 1951.

Of interest are the added examples of familial tendency to homologous periodic disorders as noted in Cases 26, 31, and 40, and elsewhere.[25] In other cases, the symptoms shifted from one system to another. Arthralgia replaced abdominalgia in Cases 1 and 41; arthralgia and abdominalgia coincided or alternated in Cases 2, 10, and 25, and in Case 24 stethalgia changed to abdominalgia. Also of interest is the unexplained predominance of periodic abdominalgia in persons of Armenian or Jewish origin, as noted before. Of the 10 new examples of abdominalgia presented or referred to here, 3 were in Armenians and 6 in Jews. The disorder is called Armenian disease in the Near East, where Armenians comprise a large proportion of the population. Studies on over 70 cases in this region are under way and will be presented later.

Thus far, except for symptomatic relief caused by salicylate compounds in some patients, therapy usually is unsuccessful. Suppression of episodes was reported in one case by the use of paraaminobenzoic acid, but no effects were noted in two of my patients or in others treated with it by physicians in Beirut. Corticotropin gave temporary relief from symptoms in a case of periodic purpura [27] but had no effect on periodic abdominalgia in Case 2 and in Case 41. Cortisone in Case 1 suppressed periodic fever for three months after therapy was stopped. It had a temporary suppressive effect in Querido's patient and none in several other patients. The symptoms in several patients with periodic neutropenia were relieved after splenectomy, but the neutropenic rhythm was unchanged.

SUMMARY

Cases of periodic disorders described in previous publications have been observed for several years more. They persist without striking changes. Therapy with cortisone modified the symptoms temporarily in one patient but did not interfere with the rhythm. New cases of the kinds already described were studied, and a number of examples of recurrent dermal, respiratory, and neurologic disorders and periodic sialorrhea were added to the list. No progress was made in discovering the cause of periodic disease, which seems to represent an inherent rhythm that provokes disturbances of widely different nature, depending on the organs or systems involved.

25. Reimann, H. A., and Angelides, A. P.: Periodic Arthralgia in 23 Members of 5 Generations of a Family, J. A. M. A. **146**:713-716 (June 23) 1951.

26. Footnote deleted.

27. Stefanini, M.; Roy, C. A.; Zannos, L., and Damashek, W.: Therapeutic Effect of Pituitary Adrenocorticotropic Hormone (ACTH) in a Case of Henoch-Schönlein Vascular (Anaphylactoid) Purpura, J. A. M. A. **144**:1372-1374 (Dec. 16) 1950.

TRANSIENT ESOPHAGEAL VARICES IN HEPATIC CIRRHOSIS

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OUR PURPOSE is to present clinical material demonstrating a hitherto unreported phenomenon, the spontaneous disappearance of esophageal varices in hepatic cirrhosis. An additional group of patients, having esophageal varices secondary to hepatic cirrhosis and normal portal pressures, will be presented and their relationship to the first group discussed.

Esophageal varices play an important and dangerous role in hepatic cirrhosis. Sodeman estimates that "esophageal varices occur in 80 to 90% of patients with definite portal cirrhosis." [1] Hemorrhage from bleeding esophageal varices has been estimated to cause between one-quarter and one-third of all deaths due to cirrhosis of the liver.[2] Although the above figures do not agree entirely with our own, they serve to demonstrate the importance of the problem.

In general, agreement exists that esophageal varices are the result of elevated venous pressures within the esophageal veins.[3] In cirrhosis of the liver these increased pressures arise as a result of intrahepatic obstruction to portal outflow.[4] Based upon the knowledge of a marked mortality in hemorrhage from esophageal varices and upon the agreement that increased portal pressure is the *modus operandi* in the development of such varices, numerous surgical procedures have been developed for lowering of esophageal venous pressures.

A brief listing of surgical procedures employed in the treatment of esophageal varices is warranted as a background for our study. Procedures designed to divert

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1. Sodeman, W. A., Editor: Pathologic Physiology: Mechanism of Disease, Philadelphia, W. B. Saunders Company, 1952.

2. (*a*) McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, Arch. Path. & Lab. Med. **5**:23 (Jan.) 1928. (*b*) Bockus, H. L.: Gastroenterology, Philadelphia, W. B. Saunders Company, 1946, Vol. 3.

3. (*a*) Bockus, H. L.: Gastroenterology, Philadelphia, W. B. Saunders Company, 1946, Vol. 1, Chap. 15. (*b*) Boyd, W.: The Pathology of Internal Disease, Ed. 4, Philadelphia, Lea & Febiger, 1944, p. 321. (*c*) Linton, R. R.: Surgical Treatment of Bleeding Esophageal Varices by Portal Systemic Venous Shunts with Report of 34 Cases, Ann. Int. Med. **31**:794 (Nov.) 1949. (*d*) Sodeman.[1]

4. (*a*) Daumerie, L., and van Brussel, J.: Syndrome of Portal Hypertension, Acta gastroenterol. belg. **14**:617 (July-Aug.) 1951. (*b*) Whipple, A. O.: The Problem of Portal Hypertension in Relation to the Hepatosplenopathies (E. Starr Judd Lecture), Ann. Surg. **122**:449 (Oct.) 1945. (*c*) Sodeman.[1] (*d*) Footnote 2.

portal pressure into the systemic circuit include splenorenal anastomosis [5] and portacaval shunting.[6] Diversion of arterial blood from the portal bed has been attempted by splenectomy.[7] Direct attack upon esophageal varices and connecting veins has included esophagectomy and gastroesophagectomy,[8] ligation and injection of the coronary veins of the stomach,[9] and injection and ligation of esophageal varices.[10] Attempts to form adhesions and collateral circulation about the esophagus are reported.[8] Attempts have been made to reduce "shunting" between hepatic arterioles and intrahepatic radicles of the portal vein by hepatic artery ligation.[11] Omentopexy has been employed in an attempt to form collateral circulation between the portal vein venous system and the veins of the inferior vena cava system.

Success in the treatment of esophageal varices has been reported with each of the above procedures. Despite multiple reports no extensive series with long term results and control studies can be found. The patients are in general poor surgical risks, and mortality, particularly in the more extensive procedures, has been appreciable.

In considering any surgical procedure in which there is an appreciable mortality and a variable chance for success, the natural desire is to operate upon patients earlier in their disease, before physiological function is grossly disturbed and structure irreparably altered. Such a trend undoubtedly provides lower surgical mortality and increased percentages of successful results. Unfortunately such a trend leads to surgery upon the borderline patient who might never have required operation for continued freedom from difficulty.

To the best of our knowledge, no group of cases has previously been reported which demonstrates the spontaneous disappearance of esophageal varices without specific surgical intervention. Varices have been reported absent at autopsy which previously had been seen on fluoroscopy.[12] There are occasional references to spontaneous increases and decreases in portal pressures. These will be discussed later.

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5. Julian, O. C., and Dye, W. S.: Venous Shunts in Portal Hypertension, A. M. A. Arch. Surg. **63**:373 (Sept.) 1951.

6. Blakemore, A. H., and Lord, J. W., Jr.: The Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, Ann. Surg. **122**:476 (Oct.) 1945. Linton.[3c]

7. Noya Benitez, J.: Splenectomy in the Treatment of Hypersplenism and Esophageal Varices, Bol. Asoc. méd. Puerto Rico **43**:375 (July) 1951. (*c*) Whipple.[4b]

8. Seabrook, D. B.: Resection of Lower Esophagus for Bleeding Varices: Report of Case, Northwest Med. **47**:498 (July) 1948. Sheline, G. E.; Clark, D. E.; Adams, W. E., and Phemister, D. B.: Symposium on Gastroesophageal Surgery: Partial Gastroesophagectomy for Esophageal Varices, S. Clin. North America **31**:213 (Feb.) 1951.

9. Grace, E. J.: Control of Massive Esophageal Hemorrhage Secondary Vein and Injection of Sodium Morrhuate, Ann. Surg. **116**:387 (Sept.) 1942.

10. Friedberg, S. A.: Symposium on Gastroesophageal Surgery: Esophagoscopy in the Diagnosis and Treatment of Esophageal Disease, S. Clin. North America **31**:3 (Feb.) 1951. Tolan, J. F.: Esophageal Varices and Their Treatment by Injection, Laryngoscope **59**:425 (April) 1949. Moersch, H. J.: Treatment of Esophageal Varices by Injection, Proc. Staff Meet., Mayo Clin. **15**:177 (March 20) 1940. Whipple.[4b] Patterson, C. O., and Rouse, M. O.: The Sclerosing Therapy of Esophageal Varices, Gastroenterology **9**:391 (Oct.) 1947.

11. Leger, L.; Albot, G.; Oudot, J., and Zerolo, J.: Ligation of Hepatic Artery in Cirrhosis of Liver, Presse méd. **60**:176 (Feb. 9) 1952.

12. Hare, H. F.; Silveus, E., and Ruoff, F. A.: Esophageal and Gastric Varices, with Report of a Case, S. Clin. North America **28**:729 (June) 1948.

That such a phenomenon as the spontaneous disappearance of esophageal varices would be of paramount importance from a therapeutic viewpoint is obvious. The detection of the group of patients in which this may occur then becomes an essential part of the determination of the criteria for performing surgical operations upon patients with esophageal varices.

MATERIAL AND METHOD

It was for the purpose of establishing a baseline as to the natural history of cirrhosis and esophageal varices that during the past four years we have performed routine esophagograms, with special technique,[18] and esophagoscopies on all patients with hepatomegaly and abnormal liver function tests suggestive of cirrhosis. These studies have been done on 502 consecutive patients to date, and approximately 150 liver biopsies have been performed.

TABLE 1.—*Case Distribution of 502 Patients with Hepatomegaly and Abnormal Liver Function Tests*

Patients with Cirrhosis		Patients Without Cirrhosis	
Diagnosis	No.	Diagnosis	No.
Laennec's cirrhosis	370	Fat infiltration (precirrhotic)	56
Cause undetermined	28	Hepatomegaly, c/u*	13
Biliary cirrhosis	8	Hepatosplenomegaly, c/u	4
Postnecrotic cirrhosis	7	Chronic hepatitis	4
Cardiac cirrhosis	5	Granuloma of the liver	2
Hemochromatosis	1	Portal hypertension with varices, c/u	1
	419	Diabetes with hepatomegaly	1
		Inferior vena cava thrombosis	1
		Splenomegaly, c/u, with varices	1
			83

* c/u = cause undetermined.

TABLE 2.—*Incidence of Esophageal Varices in 502 Patients with Hepatomegaly and Abnormal Liver Function Tests*

	Patients with Cirrhosis, No.	Patients Without Cirrhosis, No.
Varices present	108	5
Varices not present	311	78
	419	83

Table 1 represents the case distribution of this group of 502 patients. All patients have been personally examined by one of us, and we all concurred in the diagnosis. Table 2 represents results of over 800 barium studies and over 1,000 esophagoscopies which were performed on this group. All but 37 patients were subject to esophagograms and esophagoscopy. These 37 patients were either critically ill or refused esophagoscopy. In 17 of this group subsequent autopsy studies were made, giving us a "missed group" of only 20 out of 502 patients. As Table 2 shows, 113 out of the total of 502 patients were found to have esophageal varices, or approximately 22%. Of this group, we are presenting 12 patients and mentioning 3 additional patients whose varices disappeared under varied conditions. All these patients were considered to have cirrhosis of the liver or to be in a precirrhotic phase on clinical grounds.

Special precautions were necessary to be certain whether varices were or were not present. From the x-ray point of view these are to be described in another paper, but esophagoscopic errors can likewise occur.[13] In the presently reported group of patients, therefore, two observers were required to confirm or deny the presence of esophageal varices on esophagoscopy. Before

13. Kirsh, I. E.; Blackwell, C. C., Jr., and Bennett, H. D.: Roentgen Diagnosis of Esophageal Varices, to be published.

esophageal varices were diagnosed in the present group of patients, the findings had to be in agreement both on x-ray and esophagoscopy or upon esophagoscopy on two different occasions. Any exceptions to these rules will be noted individually. The clinical histories are presented at some length, so that others may be enabled to detect any common clinical features we may have missed.

REPORT OF CASES

CASE 1.—W. B. C., a 61-year-old white male railroad switchman, was first seen Nov. 9, 1951, at which time he complained of generalized weakness which had lasted for a period of approximately two months. The patient was a confirmed alcoholic. Examination on admission revealed a firm nontender liver extending two to three fingers below the right costal margin. There was no splenomegaly, ascites, or evidence of collateral abdominal circulation. There was 1+ edema in both lower extremities. There were scattered spider nevi and bilateral gynecomastia. Liver function tests were performed.[14] The cephalin flocculation was 3+ in 24 hours and 4+ in 48 hours; thymol turbidity ranged from 5 to 7 units; alkaline phosphatase varied between 3.1 and 6 Bodansky units; serum bilirubin was 0.6 to 0.9 mg. per 100 cc. Quick prothrombin time was 16 seconds, or 41.5%. During therapy this rose to 57%. The albumin: globulin ratio varied between 3.6: 3.4 and 3.0: 3.0.

X-rays of the esophagus with special technique [13] revealed densities considered to be compatible with esophageal varices. The esophagoscopists reported that "at a level of 37 cm. there were moderately large varices on the lateral and anterior walls. The cardia was 41 cm. from the upper incisor margins."

A liver biopsy was performed, using the Vim-Silverman needle, and the specimen obtained revealed distortion of the normal liver parenchymal architecture, strands of fibrous tissue separating the liver parenchyma into pseudolobules, minimal bile duct proliferation, and infiltration by histiocytes in the portal fields. The pathological diagnosis was cirrhosis; however, a definite differential diagnosis between postnecrotic cirrhosis and portal cirrhosis could not be made. No surgery was performed.

The patient was discharged on conservative therapy with a diagnosis of Laennec's cirrhosis of the liver with esophageal varices.

The patient was again admitted on Jan. 28, 1952, with no additional complaints. The liver remained enlarged three fingerbreadths below the right costal margin; the spleen was not palpable. The findings were otherwise the same. X-rays of the esophagus revealed esophageal varices, and esophagoscopy confirmed the presence of varices beginning at 36 cm. from the incisor teeth. Liver function tests were repeated. Thymol turbidity was 8 units, serum bilirubin 1.7 mg. per 100 cc., albumin: globulin ratio 3.4: 3.9, alkaline phosphatase 4.2 units, and prothrombin time 17 seconds, or 36.5%.

The patient was readmitted on April 28, 1952, for reexamination. At that time he had no complaints although he continued to rest at home. He had abstained from alcoholic intake. There had been no hematemesis and no melena, but weakness persisted. Examination at that time again revealed hepatomegaly, of three fingerbreadths. The spleen was not palpable and there was no icterus or ascites.

Liver function tests were repeated. Thymol turbidity was 8 units, and serum bilirubin 1.0 mg. per 100 cc.; platelets were normal; the prothrombin time was 16 seconds, or 41.5%; total proteins were 7.9 gm. per 100 cc. No studies were done at that time to confirm or deny the diagnosis of esophageal varices.

Reexamination on July 30, 1952, revealed no essential change in symptoms. However, physical examination revealed an absence of gynecomastia and spider nevi. Ankle edema was present (1 to 2+) and the liver remained palpable two to three fingerbreadths below the right

14. Normal values for liver function tests in our laboratory are as follows: alkaline phosphatase, 2 to 4 Bodansky units; serum bilirubin, 0.5 to 1.0 mg. per 100 cc., cephalin flocculation test, 0 in 24 hours, 1 in 48 hours or less; thymol turbidity 2 to 4 units; prothrombin time (Quick) 13 seconds (100%); sulfobromophthalein (bromsulphalein) retention, 5 mg. per kilogram, less than 5% retention in 45 minutes; albumin: globulin ratio more than 1: 1, with albumin over 3.5 mg. per 100 cc.; icterus index 4 to 6 units; cholesterol total 150 to 250 mg., cholesterol esters 80 to 150 mg., urinary urobilinogen (Watson) 0.2 mg. per 100 cc.

costal margin. Liver function tests were carried out. The albumin : globulin ratio was 3.3 : 3.5, serum bilirubin 1.4 mg. per 100 cc., thymol turbidity 10 units, and prothrombin time 48%. Esophagoscopy failed to reveal the presence of esophageal varices, and the patient was scheduled for another esophagoscopy at a later date.

Final examination was made on Oct. 8, 1952, at which time the symptoms were unchanged. The liver was no longer palpable, the spleen was not palpable, and there was no edema. Thymol turbidity was 7.6 units; sulfobromophthalein retention was 20% in 45 minutes, using 5 mg. per kilogram, prothrombin time was 14 seconds, or 57%, and serum bilirubin was 0.9 mg. per 100 cc. Esophagoscopy was again done, and again no varices could be visualized.

Summary.—A chronically alcoholic white man with persistent hepatomegaly and cirrhosis confirmed by liver biopsy had esophageal varices demonstrated both by x-ray and by esophagoscopy two times, these being moderately large and multiple. Two subsequent examinations demonstrated disappearance of these varices without intervening surgical therapy.

CASE 2.—F. D., a 54-year-old white male truck driver, was admitted to the hospital on Aug. 17, 1951. He gave a history of marked alcoholism lasting for three weeks, and he suffered from generalized abdominal cramps, extreme nervousness, and weakness and pain in both legs; the urine was dark.

Physical examination revealed an obese white man. The liver was palpable four fingerbreadths below the right costal margin and was smooth and tender. The spleen was not palpably enlarged, and there was no fluid wave. Findings compatible with peripheral neuritis were noted.

Laboratory studies revealed a red cell count of 4,560,000 and white cell count of 8,950, with a normal differential count. Serologic studies showed no abnormalities. Albumin : globulin ratio was 4.7 : 2.0. Blood urea nitrogen was 15 mg. per 100 cc. Cephalin flocculation was negative. Thymol turbidity was 1 unit, sulfobromophthalin (Bromsulfalein) showed 13% retention (5 mg. per kilogram in 45 minutes) on admission and no retention 10 days after admission. Alkaline phosphatase was 2.2 Bodansky units; serum bilirubin was 0.6 mg. per 100 cc. Chest x-ray showed no abnormalities. Barium swallow showed esophageal varices. Esophagoscopy confirmed the presence of varices at 26 cm. from the incisor teeth.

The patient was treated with a high-protein, high-carbohydrate diet and supplemental vitamin therapy in addition to mild sedation. Bed rest was prescribed. On this regimen the symptoms regressed markedly, and the patient was discharged on Sept. 17, 1951, greatly improved. The patient was recalled for reevaluation on Oct. 20, 1951. During the interim he had been feeling well and there had been no recurrence of previous symptoms. He had refrained from drinking alcoholic beverages.

Physical examination revealed the liver palpable three fingerbreadths below the right costal margin, smooth and nontender. The spleen was not palpable. Serum bilirubin, prothrombin time, thymol turbidity, and alkaline phosphatase were all within normal limits. Esophagoscopy was repeated, and the varices previously visualized could no longer be seen. Needle biopsy of the liver was performed and revealed mild fatty metamorphosis.

Summary.—An alcoholic white man with hepatomegaly but no splenomegaly and only minimal liver function abnormalities was found to have extensive esophageal varices both on x-ray examination and esophagoscopy. One and a half months later esophagoscopy failed to reveal varices. Liver biopsy demonstrated fatty infiltration of the liver.

CASE 3.—F. C. was first seen March 27, 1950, at which time a diagnosis of Laennec's cirrhosis was established on the basis of history and laboratory studies. Hepatomegaly, splenomegaly, and esophageal varices were noted on x-ray examination and esophagoscopy. The patient was found to have arteriosclerotic heart disease with cardiac enlargement. The patient was again seen July 11, 1952, having refused splenorenal anastomosis on the previous admission. At that time he was completely asymptomatic except for generalized weakness. He denied nausea, vomiting, melena, or hematemesis. The patient returned to the hospital requesting surgery.

Physical findings were essentially unchanged. The liver was palpable four to five fingerbreadths below the right costal margin and was firm and nontender. The spleen was easily palpable three to four fingerbreadths below the costal margin and was slightly tender. There were moderate ascites and a slight distention of the abdominal collateral veins. Numerous spider nevi were noted.

Laboratory studies revealed normal urine and a red cell count of 4,830,000, with 14 gm. of hemoglobin. The white cell count was 8,900, with a differential cell count of 74% polymorphonuclear leucocytes and 26% lymphocytes. Liver function studies revealed an albumin: globulin ratio of 3.5: 3.5; prothrombin time on two occasions was 29.2% and 36.5%. Alkaline phosphatase was 5.6 units, thymol turbidity 11 units, and cephalin flocculation 4+ and 4+. Sulfobromophthalein retention was over 50% in 45 minutes. Serum bilirubin was 3.2 and 3.3 mg. per 100 cc. Barium swallow showed no esophageal varices. Esophagoscopy on July 30, 1952, failed to reveal any esophageal varices. No surgery was performed. Repeat esophagoscopy on March 7, 1953, following a bout of melena, again failed to reveal varices.

Summary.—A patient with clinical Laennec's cirrhosis with no history of hematemesis or melena refused surgery for varices demonstrated both by x-ray and by esophagoscopy but returned later requesting surgery. X-rays and esophagoscopy two years after the first examinations failed to reveal any persistence of varices. Melena subsequently occurred, but varices were again absent.

Case 4.—F. Mc.D., a 55-year-old white man, was admitted June 13, 1952, with ulcer-like symptoms and emesis of a small amount of reddish-brown material. He admitted to heavy alcoholism. Examination revealed hepatomegaly, of 7 cm. below the right costal margin, and splenomegaly, of 3 cm. below the left costal margin. There were a few scattered spider nevi but no fetor hepaticus, gynecomastia, or collateral abdominal circulation.

Results of liver function tests were as follows: thymol turbidity 3 units, cephalin flocculation negative, sulfobromophthalein retention 20%, van den Bergh 0.1 mg. direct-reacting and 0.5 mg. indirect-reacting bilirubin, prothrombin time 48%, cholesterol 212 mg. and cholesterol esters 155 mg. per 100 cc. Barium esophagram revealed esophageal varices, and esophagoscopy confirmed their presence. Duodenal ulcer was found on x-ray.

No surgery for relief of portal hypertension was done, because of doubt of the source of bleeding.

The patient returned on Dec. 15, 1952, with essentially the same complaints but no hematemesis. He had refrained from drinking but had inadequately followed an ulcer regimen. Physical findings were unchanged. Prothrombin time was 41.5%, nonprotein nitrogen 30 mg. per 100 cc., thymol turbidity 3 units, alkaline phosphatase 3.9 units, sulfobromophthalein retention 19%, albumin 4.1 gm., globulin 2.7 gm., van den Bergh 0.6 mg. direct-reacting and 0.7 mg. indirect-reacting bilirubin, cephalin flocculation 0 and 1+, total cholesterol 226 mg. and cholesterol esters 165 mg. per 100 cc. Gastric analysis showed 40 units total acid and 20 units free acid. Barium studies revealed slight serration suggestive of varices; esophagoscopy failed to reveal varices. Duodenal ulcer was again seen on x-ray.

Summary.—A chronic alcoholic had hepatosplenomegaly, esophageal varices demonstrated both by x-ray and by esophagoscopy, liver function abnormalities of slight degree, and symptoms and roentgen findings of duodenal ulcer. Later esophagoscopy by two men failed to reveal varices.

Case 5.—P. J. M., a 43-year-old white man, first was seen Jan. 5, 1951, because of emesis, poor appetite, and 50 lb. (22.5 kg.) weight loss. He consumed 1 to 1½ pints (0.47 to 0.68 liters) of "wine" daily. There had been no hematemesis, but he had occasional tarry stools. He demonstrated mild delirium tremens, the sclera were icteric, and the liver was palpable 4 cm. below the right costal margin. Minimal ascites was present. Peripheral neuropathy was noted. Laboratory tests revealed that the albumin: globulin ratio was 3.5: 3.4, thymol turbidity 5 units, alkaline phosphatase 6.9 to 8.4 units, van den Bergh 5.4 mg. direct-reacting and 9.4 mg. total bilirubin, dropping to 0.6 mg. direct-reacting and 1.6 mg. total. Barium swallow was normal; however, esophagoscopy revealed a single "possible" varix at 6 o'clock on the posterior wall 39 cm. from the upper incisor teeth.

The patient returned on May 2, 1951, in shock, having had massive hematemesis and melena. A Sengstaken tube[15] was used to control bleeding and 4,500 cc. of whole blood was administered. The liver was 4 cm. enlarged, and the spleen was palpable. Liver function tests revealed thymol turbidity 2 units, alkaline phosphatase 3.8 units, sulfobromophthalein retention 28%, albumin: globulin ratio 4.4: 3.7, van den Bergh 1.7 mg. direct-reacting and 1.8 mg. total bilirubin, and cephalin flocculation negative. Upper gastrointestinal series failed to reveal pathology. Esophagoscopy revealed a single varix at 5 o'clock on the posterior wall at 39 cm. from the upper incisor teeth. No surgery was performed.

The patient returned on Feb. 20, 1952, and Aug. 26, 1952; on each of these occasions esophagoscopy failed to reveal any varix. The patient has had no further bleeding and has avoided alcohol since the episode of hematemesis. Liver function has shown continued improvement; on Feb. 20, 1952, cephalin flocculation was negative, alkaline phosphatase 3.9 units, thymol turbidity 4 units, serum bilirubin 1.5 mg., and albumin: globulin ratio 4.0: 3.2. On the last examination the liver was palpable 1 cm. below the right costal margin on deep inspiration and the spleen was not palpable.

Summary.—In a patient with clinical Laennec's cirrhosis a varix of the esophagus was demonstrated at the same site two different times by two different esophagoscopists and later was not demonstrated at two different times by the same men.

Comment on Cases.—These first five cases illustrate definitely established esophageal varices which subsequently disappeared without any intervention other than medical therapy. In Case 1 alteration of liver disease was demonstrated by the disappearance of a liver edge previously palpable 2 to 3 cm. from the costal margin. The esophageal varices, however, had disappeared prior to such shrinkage. In Case 2 some questionable decrease in liver size was demonstrated, but particularly notable is the presence of fat infiltration on liver biopsy. Liver dysfunction was only mild from the onset. In Case 3 there was no evidence of regression or alteration of the pattern of liver disease; there was only the disappearance of previously established varices. Of note is the fact that none of these 3 patients had bleeding in the form of hematenesis or melena. This type of condition would, then, be discovered only in the course of routine esophagoscopy and barium studies of all patients with cirrhosis. Only in Case 3 was there ascites, and this was noted after the varices had disappeared. In Case 4 there was bleeding of uncertain cause (either varices or ulcer, most probably the latter); in this case varices disappeared despite lack of evident change in liver status. In Case 5 there was bleeding, apparently from a single esophageal varix, which disappeared after a period of abstinence from alcohol. The patient had severe hemorrhage on May 2, 1951; however, the varix was still present after the hemorrhage and was not found to have disappeared until seven months later. The varix has not recurred. Marked reduction in liver size and a return of liver function to normal were concomitantly noted.

CASE 6.—O. J. L., a 58-year-old white male painter, was hospitalized on two occasions, Dec. 15, 1945, and Jan. 15, 1947, with massive hematemesis and melena and symptoms of pyrosis suggestive of peptic ulceration. No positive x-ray diagnosis could be established. In August of 1946, however, hepatomegaly, of 2 cm., and a palpable splenic tip were noted. He denied alcoholism. He was admitted Jan. 15, 1947, with a four-day history of severe hematemesis. Examination revealed hepatomegaly, 2 cm., and no splenomegaly. Stools were positive for

15. Sengstaken, R. W., and Blakemore, A. H.: Balloon Tamponage for Control of Hemorrhage from Esophageal Varices, Ann. Surg. **131**:781 (May) 1950. Bennett, H. D.; Baker, L., and Baker, L. A.: Complications in the Use of Esophageal Compression Balloons (Sengstaken Tube), A. M. A. Arch. Int. Med. **90**:196 (Aug.) 1952.

blood. The red cell count was 2,480,000, and hemoglobin was 7.5 gm. per 100 cc. The white cell count, differential cell count, prothrombin time, and cephalin flocculation were normal. Albumin: globulin ratio was 3.8:3.5 gm., sulfobromophthalein retention 18% in 45 minutes, icteric index 6.6, and serum bilirubin 0.5 mg. per 100 cc. Thymol turbidity was 15 units. Repeat gastrointestinal series was again normal. Results of special studies[9] of the esophagus with thick barium were suggestive of esophageal varices. Barium enema showed no abnormalities. Esophagoscopy revealed that "the entire esophagus below the cricopharyngeus is involved by large esophageal varices, some of which are covered with dry blood." A presumed perforation of the esophagus occurred, but the resulting mediastinitis cleared with conservative therapy.

The patient was readmitted Dec. 12, 1949, with a recurrence of melena and gnawing epigastric pain not relieved by antacids. The liver was enlarged 2 cm.; the spleen was not palpable. There was no ascites. No change in liver function tests was noted. Esophagoscopy was not repeated. Ulcer type of management was given, with relief of symptoms.

A recurrent hematemesis and melena led to readmission on July 30, 1950. All studies and findings were unchanged. Both esophagoscopy and gastroscopy failed to reveal any evidence of varices at this time.

The patient was readmitted on Dec. 10, 1950, with a two-day history of melena. Upper gastrointestinal studies revealed no varices, but a questionable duodenal deformity was noted.

A right benign gynecomastia was removed in April, 1951. Repeat esophagoscopy at that time failed to reveal esophageal varices; however, a small esophageal diverticulum was now noted (site of previous perforation?). Exploratory laparotomy was performed, and a cirrhotic nodular liver was noted. The spleen and upper gastrointestinal tract were normal in appearance. A clinical impression of increased pressure in the portal system was obtained, but no pressure measurements were taken.

The last admission was Sept. 8, 1951, because of a two-day history of melena. The liver was palpable 2 cm. below the right costal margin; the spleen was not palpable. Red blood cell count was 2,900,000. Prothrombin time was 14 seconds, or 57%. Cephalin flocculation was 2+ and 3+. Thymol turbidity was 7 units, sulfobromophthalein retention was 14% in 45 minutes, and alkaline phosphatase was 2.6 Bodansky units. Gastrointestinal x-rays and esophagoscopy failed to reveal esophageal varices. Liver biopsy revealed increased connective tissue and heavy round cell infiltration in the portal areas, compatible with cirrhosis of undetermined type. The patient was treated conservatively and was discharged from the hospital.

Summary.—The patient is a 58-year-old white male painter with recurrent hematemesis and massive esophageal varices proved both by x-ray and esophagoscopy in 1947, which subsequently disappeared. Mediastinitis secondary to perforation of the esophagus in 1947 is a complicating factor.

CASE 7.—J. McC., a 46-year-old white man, was admitted on June 26, 1950, with a four-month history of swelling of the abdomen and legs and jaundice and a history of diarrhea of six days' duration. Weakness, anorexia, and a tendency to bruise easily had been present since the onset of the illness. There was a history of excessive alcoholism throughout his entire adult life.

Physical examination revealed marked jaundice, distention of the abdomen, and bulging of the flanks. A fluid wave and shifting dullness were noted. The liver was palpable nine finger-breadths below the right costal margin and was markedly tender. The spleen was not palpably enlarged. There was 3+ pitting edema of both lower extremities.

Laboratory examinations revealed a red cell count of 3,900,000 and a white cell count of 17,000, with polymorphonuclear leucocytes 82%, lymphocytes 16%, and eosinophiles 2%. Serum bilirubin was 7.8 mg. per 100 cc., thymol turbidity 3 units, and total protein 5.6 gm. per 100 cc., with an albumin: globulin ratio of 2.4: 3.2. Alkaline phosphatase was 8.5 Bodansky units, and cephalin flocculation was 3+ in 24 hours and 4+ in 48 hours. Urinary urobilinogen was 1.2 mg. per 100 cc. Prothrombin time was 15 seconds, or 57%. Gastrointestinal studies with special studies of the esophagus revealed the presence of esophageal varices. Esophagoscopy confirmed the presence of esophageal varices on the posterior and anterior lateral walls, extending downwards from 32 cm. below the upper incisor teeth.

The patient responded well to a regimen of bed rest and a high protein, high carbohydrate diet with supplementary vitamin therapy. During the hospital stay results of liver function tests improved but did not become completely normal. Ascites disappeared. The patient was esophagoscoped again during hospitalization, with intention of injecting the varices with sclerosing solution; however, at that time there was noted an esophagitis as well as varices of the lower esophagus and the procedure was postponed. The patient was recalled to the hospital on Nov. 27, 1950, to have the esophageal varices injected with sclerosing solution. At the time of esophagoscopy, however, it was noted that the esophageal varices had disappeared, except for an exceedingly questionable small varix just above the cardia. The patient stated that he felt well. Liver function studies were again performed and all results were normal, except for a serum bilirubin level of 2.8 mg. per 100 cc.

Summary.—A case is presented of clinical Laennec's cirrhosis with varices proved on two occasions, which disappeared following esophagitis and concomitant improvement of liver function.

Comment on Cases.—Cases 6 and 7 bear great similarity to each other in that each patient had inflammatory disease of the esophagus and surrounding tissues along with cirrhosis. In Case 6 the patient suffered recurrent massive bleeding, with two possible etiological sources, namely, peptic ulceration and esophageal varices. The presence of blood clots on the varices makes bleeding from these sites presumptive. Perforation of the esophagus with resultant mediastinitis preceding the disappearance of varices makes this a possible etiological agent in their disappearance. This will be discussed later. In Case 7 esophagitis was noted when injection of varices was contemplated, and injection was therefore delayed. The varices subsequently disappeared without injection. The possible role of esophagitis will likewise be discussed later.

CASE 8.—O. K., a 51-year-old white man, was admitted to the hospital on June 19, 1950, and gave a history of ingesting a quart (0.95 liter) of "wine" and several bottles of beer daily for a period of several years. On the night prior to admission there were several bouts of hematemesis; he vomited a total of 2 cupfuls (0.47 liter) of blood, following which he had several tarry stools. There was no previous history of gastrointestinal hemorrhage, jaundice, or liver disease.

The patient did not appear acutely ill. There were scattered vascular nevi on the face and chest. Blood pressure was 120/50, pulse rate 120. The abdomen was slightly obese. The liver was palpable four fingerbreadths below the right costal margin and was smooth and slightly tender. The spleen was questionably palpable; rectal examination revealed tarry stool.

Laboratory examinations revealed a normal urine; nonprotein nitrogen was 48 mg., later 25 mg. per 100 cc.; the albumin: globulin ratio was 3.6: 2.2. Stools revealed occult blood (4+) by the benzidine test. Bleeding time was 25 seconds, clotting time 3 minutes, platelet count 231,000, alkaline phosphatase 3.3 units, and prothrombin time 13 seconds, or 100%. Thymol turbidity and results of the quantitative van den Bergh test for bilirubin were normal. The sulfobromophthalein test demonstrated no retention in 45 minutes. On admission the red cell count was 3,650,000. Gastric analysis revealed no free acid and a total of 16 units in the fasting specimen. After administration of histamine there were 130 units of free acid. Chest x-ray was normal. Gastrointestinal studies revealed hypertrophic gastric rugi and esophageal varices. Esophagoscopy confirmed the presence of esophageal varices ("two small varices lying near the cardia, 41 cm. from the incisor teeth").

The patient was placed on conservative therapy, including bed rest and antacid therapy. Gastrointestinal hemorrhage subsided under this management within 48 hours. A total of 4 pt. (1.9 liters) of whole blood were administered during hospitalization. The liver and spleen both decreased considerably in size. On Feb. 8, 1951, an exploratory operation was done through a thoracoabdominal incision made for the purpose of doing a splenorenal anastomosis. The spleen and liver were both grossly normal. No dilated veins were seen. The splenic vein pressure was found to be 75 mm. of water. The stomach was opened and explored. No varices or other

bleeding areas were found. Because of danger of torsion of the spleen, due to mobilization required in taking pressures, a splenectomy was performed. Wedge biopsy of the liver revealed edema and scattered necrosis of the liver cells, with very minimal fat infiltration. A section of the spleen revealed no abnormalities in the spleen. The postoperative course was uneventful save for sterile pneumohydrothorax on the left. The patient was discharged on March 19, 1951, and was recalled for reexamination on June 20, 1951, at which time he was completely asymptomatic. Hepatomegaly persisted. A repeat esophagoscopy was performed, and no varices were noted.

Summary.—An alcoholic patient with hepatomegaly, hematemesis, and large esophageal varices demonstrated by both x-ray and esophagoscopy had normal splenic vein pressures. Varices were absent three months postoperatively.

CASE 9.—E. F. S., a 44-year-old white male laborer, was first seen Oct. 3, 1949, with complaints of jaundice, dark urine, abdominal swelling, and leg edema. He drank large amounts of alcohol.

Examination revealed ascites; the liver was enlarged 7 cm., and the spleen was not palpable. Liver function tests revealed thymol turbidity 7 units, alkaline phosphatase 7.4 units, 2.3 mg. direct-reacting and 3.6 mg. total bilirubin per 100 cc. The albumin: globulin ratio was 2.6: 2.6. Under treatment with bed rest, vitamins, and diet, the ascites and edema subsided but results of liver function tests remained unchanged. No x-ray of esophagus or esophagoscopy was done.

The second admission was on June 13, 1950, for delirium tremens. The liver was enlarged 4 cm.; the spleen was palpable. Liver function tests revealed progressive changes; the albumin: globulin ratio was 3.2: 4.1, thymol turbidity 12 units, cephalin flocculation 4+ in 24 hours and 4+ in 48 hours. Sulfobromophthalein retention was 17%. Barium studies of the esophagus showed no abnormalities; however, the esophagoscopists reported that "varices were seen on the anterior and posterior walls of the esophagus at a distance of 32 cm. and extending downward."

On Sept. 4, 1950, the patient returned for an attempted splenorenal anastomosis for relief of portal hypertension. There had been no hematemesis, but melena had occurred. Liver function tests revealed marked improvement: the van den Bergh test showed 0.2 mg. direct-reacting and 0.6 mg. total bilirubin per 100 cc., alkaline phosphatase was 3.0 units, and the albumin: globulin ratio was 3.6: 2.6. Thymol turbidity was 2 units; cephalin flocculation was 2+ in 48 hours. The liver was enlarged 3 cm.; the spleen was only questionably palpable. On Sept. 21, 1950, a splenorenal anastomosis was attempted but failed owing to friability of the splenic vein. The liver was granular, large, and hard. Pressures prior to ligation of the splenic artery were as follows: splenic vein, 140 mm. water; portal vein, 190 mm. water. The splenic vein was patent. Splenectomy was performed. The spleen revealed "congestive fibrosis." Postoperatively the patient had a single episode of hematemesis.

He returned Jan. 12, 1951, with no symptoms and no bleeding. The patient returned for esophagoscopy on July 11, 1951. No varices were detected. A liver biopsy specimen taken with a Vim-Silverman needle confirmed a diagnosis of Laennec's cirrhosis. Liver function tests revealed the following: cephalin flocculation negative, thymol turbidity 3 units, and cholesterol and esters 195/136 mg. The liver was not palpable.

The patient was last studied on July 18, 1952. He was working and was feeling well, save for some generalized weakness. Esophagoscopy revealed extensive varices. The liver was again palpable 2 cm. below the costal margin. Results of liver function tests were normal.

Summary.—A patient with biopsy-established Laennec's cirrhosis with melena and extensive esophageal varices was found to have normal portal and splenic vein pressures on laparotomy. Splenectomy was performed. There was a single postoperative episode of hematemesis. One year postoperatively no varices could be detected; however, two years postoperatively extensive varices were again detected.

CASE 10.—E. F., a 47-year-old white male traveling salesman, was admitted Nov. 28, 1951, because of massive hematemesis and melena. There was a history of mild recurrent epigastric distress partially relieved by soda and a history of irregular eating habits, with moderate alcohol intake. Examination revealed no evidence of jaundice, ascites, hepatomegaly, or splenomegaly.

Red cell count was 3,500,000; the white cell count, differential cell count, smear, platelets, and prothrombin times were normal. Thymol turbidity was 2 units, cephalin flocculation negative, alkaline phosphatase 6 units, and serum bilirubin less than 0.5 mg. per 100 cc. The albumin: globulin ratio was 4.3: 3.5. Bleeding and coagulation times were normal. X-ray of the esophagus and esophagoscopy revealed extensive esophageal varices 33 to 39 cm. from the incisor teeth. Gall bladder x-rays were normal.

Exploratory laparotomy in the middle of January 1952 failed to reveal portal hypertension prior to ligation of the splenic artery, although actual pressures were not taken. Splenectomy was performed, and a hiatus hernia was repaired. Liver sections revealed slight increases of fibrous tissue, round cell infiltration, and moderate fat infiltration; the spleen revealed passive congestion.

Repeat x-rays and esophagoscopy two weeks postoperatively revealed no esophageal varices.

Summary.—A 47-year-old white man with hematemesis, melena, and proved esophageal varices demonstrated both by x-ray and esophagoscopy was found to have normal portal pressures on laparotomy; postoperatively the varices disappeared. Both splenectomy and repair of esophageal hiatus hernia were done. Liver biopsy revealed changes compatible with early cirrhosis.

CASE 11.—M. M., a 31-year-old white laborer who normally ingested 1 qt. (0.95 liter) of whiskey daily, had hematemesis Jan. 6, 1952. There was no known previous illness. At the time of admission the patient was in a state of delirium tremens. The liver was enlarged 3 cm.; no splenomegaly or ascites was noted. The patient vomited 1,000 cc. of blood during the examination.

The initial red cell count was 3,600,000; hemoglobin was 10.5 gm. The white blood cell count, differential count, serology, and prothrombin time were within normal limits. Cephalin flocculation was 1+ and 3+, thymol turbidity 2 units, alkaline phosphatase 3.8 units, and there was 0.15 mg. direct-reacting and 0.5 mg. total bilirubin. The albumin: globulin ratio was 4.3: 3.3. X-rays of the esophagus and esophagoscopy revealed extensive esophageal varices from 34 to 39 cm. below the incisor teeth.

A Sengstaken tube was employed with good results to control bleeding, and on March 13, 1952, exploratory laparotomy was performed with the intention of accomplishing a splenorenal anastomosis. The liver appeared edematous but otherwise normal. The portal vein appeared patent, and direct measurements revealed a pressure of 150 mm. of water. Splenectomy was not performed. Liver biopsy revealed mild fatty metamorphosis. Esophagoscopy at the time of surgery confirmed the presence of esophageal varices.

Summary.—A 31-year-old white male alcoholic had esophageal varices proved by x-ray examination and esophagoscopy in January 1952. Massive hematemesis and melena occurred the day before and the day after admission. Exploratory laparatomy on March 13, 1952, failed to reveal portal hypertension. Esophageal varices were still present, as demonstrated by esophagoscopy done at the time of surgery.

CASE 12.—C. K., a 37-year-old white male laborer, was first admitted to the hospital on Oct. 3, 1949, with a history of severe jaundice six months previously, which had subsided spontaneously in six to seven weeks. For one week prior to admission he noted progressive swelling of the legs, which extended as high as the abdomen. He gave a history of heavy alcoholic intake all his adult life, with an average intake of 7 to 8 pt. (3.29 to 3.76 liters) of "wine" per day for the past one and one-half years.

Physical examination on admission revealed a moderately obese acutely ill white man with mild icterus and marked abdominal distention. A fluid wave and shifting dullness were present. No organs could be palpated because of marked ascites.

Laboratory studies revealed anemia (2,400,000 red cells), hemoglobin 7.5 gm., and white cell count 4,200, with a normal differential cell count. Urinalysis and serology showed no abnor-

malities. The albumin : globulin ratio was 2.6 : 2.6. Thymol turbidity was 4 units, alkaline phosphatase 7.4 units, bilirubin 2.3 mg. (direct reacting) and 3.6 mg. (total) per 100 cc., and cephalin flocculation negative. Chest x-ray was reported as showing no abnormality.

The patient was kept on absolute bed rest and was given a high-protein high-carbohydrate low-sodium diet. He was given 500 cc. of whole blood shortly after admission. On this regimen the patient's edema and ascites gradually disappeared. An abdominal examination revealed the liver then to be palpable 6 to 7 fingerbreadths below the right costal margin; the spleen was not palpable. During hospitalization the red cell count gradually increased to 4,150,000 and the albumin : globulin ratio became 4.5 : 3.6.

The patient was readmitted on April 18, 1950, in delirium tremens. Subsequent history revealed marked alcoholic intake for three weeks prior to admission.

Physical examination revealed an acutely ill white man with delirium tremens. The liver was palpable 4 fingerbreadths below the right costal margin. There were no spider nevi upon the upper thorax; the spleen was not palpable.

Laboratory data revealed the complete blood count to be within normal limits. Gastric analysis revealed achlorhydria. The albumin : globulin ratio was 3.2 : 4.1, thymol turbidity 12 units, cephalin flocculation 4+, quantitative bilirubin determination 3.7 mg. direct-reacting and 5.8 mg. total per 100 cc. The sulfobromophthalein test revealed 17% retention in 45 minutes, using 5 mg. per kilogram. Esophagoscopy revealed varices at the lower end of the esophagus. Close questioning revealed an episode of liquid foul-smelling black stools on one occasion, lasting for two days.

The patient was discharged on a high-protein high-carbohydrate diet and was recalled to the hospital Sept. 4, 1950, for a splenorenal anastomosis. On Sept. 21, 1950, this operation was attempted, but it could not be accomplished because of several friable areas in the splenic vein. The portal pressure on direct measurement was 200 mm. of water, and the pressure in the splenic vein was 140 mm., prior to ligation of the splenic artery. Postoperatively the patient had one episode of coffee-ground emesis, but the postoperative course was otherwise uneventful. The spleen was removed at the time of surgery.

The patient returned for reexamination July 10, 1951, at which time an esophagoscopy was repeated and the previously visualized varices had disappeared.

Physical examination showed no essential change from previous examination. Liver biopsy specimen taken with a Vim-Silverman needle revealed changes compatible with Laennec's cirrhosis.

The patient was again seen Jan. 14, 1952. At that time he stated he felt well except for occasional nervousness and nausea before arising in the morning. There have been no recurrences of gastrointestinal hemorrhages, ascites, or edema.

Physical examination showed vascular nevi. The liver was barely palpable below the right costal margin. There was no ascites.

Summary.—A known alcoholic patient with biopsy-proved Laennec's cirrhosis and esophageal varices was found to have normal portal pressures upon laparotomy, and the varices disappeared postoperatively.

Comment on Cases.—The preceding five cases all represent patients operated upon for the relief of portal hypertension causing esophageal varices; in Cases 7 to 10 the patients had suffered gastrointestinal hemorrhage. The portal pressure of each was found to be normal. Splenectomy was performed in each case, except Case 11, and may well have contributed to the disappearance of varices, although they might have been on the way toward spontaneous disappearance. In Case 9, it will be noted, varices recurred two years postoperatively.

In addition to the 12 cases reported above we have seen three patients who seemed to demonstrate the nonsurgical disappearance of esophageal varices. These have been omitted from this report for one or more of the following reasons: (1) uncertainty upon the part of the esophagoscopists as to their findings, (2) our

failure to obtain confirmation by a second esophagoscopist, (3) the extremely small size of varices noted, so that we felt there might be a chance for error although the esophagoscopists felt that there was no question of the presence of the varices.

GENERAL COMMENT

If the phenomenon of the disappearance of previously established esophageal varices is accepted on the basis of the material we have presented, the questions arise as to how this may come about and, finally, what is the clinical import. The following discussion is primarily concerned with these two questions.

There seems little reason to attack the basic premise that the esophageal varices in hepatic disease are due to increased pressure within the portal venous system. Direct measurements of these pressures have been done repeatedly by ourselves and others and have been found almost invariably elevated.[16]

That local obstruction to venous return can cause esophageal and gastric varices is undoubted. This is supported by multiple reports of gastric and esophageal varices in thrombosis of coronary and gastric veins, carcinoma of the stomach, gastric ulcer, carcinoma of the pancreas, and even esophagitis.[17] These factors, however, appear to play a minor part, if any, in the average case of hepatic disease causing esophageal varices.

Most investigators agree that portal hypertension in liver disease is caused by increased resistance to outflow from the portal vein. Herrick emphasizes intrahepatic shunting between the hepatic arterioles and intrahepatic portal venules.[18] Others feel that intrahepatic pressure and distortion of the liver parenchyma play an important role.[19] A very fine discussion of this problem is to be found in Whipple's article [4b] and will not be reviewed here.

Whipple has pointed out that "the degree of portal hypertension varies in the different types of cirrhosis and in the patients with the same type of cirrhosis, and varies in the same individual with cirrhosis at different times."[4b] It is this concept of the variability of portal pressures that constitutes the theoretical background for the clinical phenomena we have reported. Such fluctuations may be a factor in precipitating hemorrhage in patients with esophageal varices. Corollary evidence exists in the well-known reductions and increases in the size of the spleen during treatment and in exacerbations of cirrhosis of the liver. It is recognized that pulp hyperplasia may well play a part in this picture.[8b] In the discussion to follow we hope to bring out some of the factors that may play a part in this fluctuating portal hypertension.

Changes in hepatic size during the course of hepatic disease are well known. The liver has a capsule composed of fibrous tissue and a basic supporting mesen-

16. Bellis, C. J.: Portal Venous Pressure in Man, Proc. Soc. Exper. Biol. & Med. **50**:258 (June) 1942.

17. Marks, L. J.; Weingarten, B., and Gerst, G. R.: Carcinoma of the Tail of the Pancreas Associated with Bleeding Gastric Varices and Hypersplenism, Ann. Int. Med. **37**:1077 (Nov.) 1952. Weinberg, T.: Observations on Occurrence of Varices of Esophagus in Routine Autopsy Material, Am. J. Clin. Path. **19**:554 (June) 1949.

18. Herrick, F. C.: An Experimental Study into the Cause of the Increased Portal Pressure in Portal Cirrhosis, J. Exper. Med. **9**:93, 1907.

19. (*a*) Cates, H. B.: Subacute Alcoholic Cirrhosis with Hemorrhage from Esophageal Varices with Reference to Portal Hypertension and Therapy, Am. J. Digest. Dis. **20**:3 (Jan.) 1953. (*b*) Whipple.[4b]

chymal structure. To distend and enlarge the liver must of necessity require pressure. This pressure would be exerted equally against all structures, but the compressible vascular system would no doubt be affected prior to the stretching of the less malleable fibrous matrix and capsule. The vascular components of the liver under the least hydrostatic pressure would be expected to be the first affected. Only late and under extreme pressures would the arterial vascular system suffer appreciably.

Increases in size and pressures within the liver can be brought about through changes in the volume and structure of a number of components: (1) parenchymal liver cells, through inflammation, edema, and fat infiltration[20]; (2) increased volume, caused by inflammatory cells; (3) regeneration of liver cells, with resulting pressure and distortion of vascular channels. Cases 1 to 5 conceivably represent such phenomena; however, alterations in collateral pattern may well play an important role, as discussed below.[21]

The presence of hepatic cirrhosis provides a particularly firm matrix in the liver, within which relatively small changes in cellular volume will exert maximal influences on portal flow. In fat infiltration of the liver, according to Moschowitz, "the swelling of the hepatic cords may be so great as to compress the sinusoids completely so that the entire lobule appears almost avascular. The intra-capsular tension is increased; this is reflected in the tense capsule, the averted cut edges and the parenchyma protruding beyond the cut surfaces."[20a] We feel that fat infiltration probably plays a major role in the phenomena of disappearing varices and fluctuating portal hypertension, whereas parenchymal distortion probably plays a more prominent role in the permanent portal hypertension found in some patients. The presence or absence of arteriovenous shunts, as described by Herrick, in no way affects this concept, as vascular compression and portal hypertension would result in either case.

Alterations in tonus within the portal system have not been demonstrated and would have to be both sustained and marked in order to affect the formation of esophageal varices, as it is not felt that increased pressures lasting only a matter of hours could cause the development of such extensive collateral circulation. More study is needed on this aspect of the problem. The portal system unfortunately is not readily available for study in humans.

It is well recognized that thrombosis of the portal vein can give rise to portal hypertension. There is, in fact, an increased incidence of such occurrences in patients with hepatic cirrhosis. A drop in such elevated pressures could conceivably come about by resolution of the thrombus in the partially occluded portal vein or by the establishment of adequate collateral circulation. Clinically, nothing to suggest such an occurrence was noted in our patients, and those operated upon showed no evidence of venous thrombosis. We therefore feel that this is not the explanation in the group of patients presented.

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20. (*a*) Moschowitz, E.: Laennec Cirrhosis: Its Histogenesis, with Special Reference to the Role of Angiogenesis, Arch. Path. **45**:187 (Feb.) 1948. (*b*) Atlas, D. H., and Kirshen, M. M.: Cirrhosis of the Liver: Natural History of a Disease, M. Clin. North America **37**:87 (Jan.) 1953. (*c*) Cates.[19a]

21. Kelty, R. H.; Baggenstoss, A. H., and Butt, H. R.: Relation of Regenerated Liver Nodule to Vascular Bed in Cirrhosis, Gastroenterology **15**:285 (June) 1950.

Increased portal pressures would conceivably arise from an increased inflow of blood from the splanchnic into the portal vessels, and a fall in pressures could result when such splanchnic vasodilatation was decreased. We have very little to offer in support or refutation of this concept. No evidence was seen of erythema of the intestines or evident splanchnic dilatation during operation on any of our patients with portal hypertension, nor is there reason to believe that this alone could cause more than extremely transient increase in pressures. This concept, then, is felt to be only of theoretical interest and not practically valid in our present state of knowledge.

Splanchnic flow is not the only source of portal blood supply and hence pressure. Estimates of from 20 to 40% of total portal flow are given for the amount of blood supplied by way of the splenic artery through the splenic vein to the portal system.[4b] It is for this reason that it was repeatedly emphasized that portal pressures were measured in Cases 8, 9, 10, 11, and 12 prior to ligation of the splenic artery. Splenectomy may well have been a major contribution to the disappearance of varices in these patients. The presence of normal portal pressures at the time of surgery leaves open the question as to whether these patients were not on their way to the spontaneous disappearance of varices prior to surgery.

Alterations in degree and site of collateral circulation probably play a very important part in the etiology of fluctuating portal pressures. In our own series of patients we have repeatedly noted the development and fluctuation in degree of abdominal collateral circulation in patients other than those described herein. Although the patients described in this report demonstrated no fluctuations in external abdominal collateral circulation, enlargement of internal collateral circulation is possible. If collateral circulation of sufficient caliber develops elsewhere than in the esophagus, portal pressure may be reduced sufficiently to allow for the collapse of esophageal varices.[22] The increased resistance within esophageal veins resulting from injection of sclerosing injections by way of the esophagoscope and the resultant development of collateral circulation elsewhere probably accounts for the success reported with this procedure.

Attempts to develop collateral circulation about the esophagus by means of surgically induced inflammatory changes have been previously mentioned. Because this same process might conceivably occur naturally, Cases 6 and 7 in the present series were separated from the first five clear-cut cases of the spontaneous disappearance of esophageal varices. Infection secondary to esophagitis was present in Case 7 and a mediastinitis developed secondary to esophageal perforation in Case 6. Such inflammation might act in one of several ways to eliminate esophageal varices. 1. Esophagitis might have caused the varices, and subsiding of the esophagitis might allow the varices to disappear. 2. Esophagitis might obliterate preexisting varices by direct inflammatory involvement of the veins. 3. Periesophageal collateral circulation might develop in the inflammatory areas, allowing for an appreciable reduction in venous pressures and resulting collapse of esophageal varices in the submucosal veins.

In the hope of detecting common clinical characteristics in the patients demonstrating the spontaneous regression of esophageal varices, an analysis of the histories, laboratory findings, and physical findings has been made. The following general characteristics have been noted. 1. These patients all ceased drinking. 2.

22. Kaplan, B.: Esophageal Varices, M. Rec. **154**:176 (Sept.) 1941.

The liver function improved in the majority. 3. Splenomegaly was rare, and ascites was even more rare. 4. Liver size usually decreased during the period of observation. Liver damage varied from severe to mild but in general tended to be less severe than in the control group with varices. Hemorrhage occurred in five of the surgically treated patients but in only two of the patients not operated on. This is to be expected, as the presence of hemorrhage and esophageal varices was in general taken as a criterion for surgical intervention.

This group of patients with spontaneously disappearing esophageal varices should be of increasing importance to the internist and surgeon evaluating patients for the surgical relief of portal hypertension. Portal hypertension per se without the presence of esophageal varices causes few, if any, symptoms. We feel that surgery is warranted in portal hypertension only for the freedom offered from hemorrhage and not for ascites alone. Our success in the surgical relief of ascites has been less than that obtained under medical management. These patients all fall within a poor-risk group, and any unnecessary surgery should be strictly avoided.

Although these patients had in common certain clinical characteristics, these same characteristics were unfortunately found in many patients who had no varices or whose varices persisted despite medical therapy. This fact has forced us to depend upon repeated esophagoscopy in order to detect a decrease in the size of or disappearance of esophageal varices prior to surgery. If esophageal varices are decreasing in size, it is probably best to postpone surgery until stability in the size and extent of varices has been established. Although we still assume that the splenorenal anastomosis or portocaval anastomosis represents the treatment of choice for patients having bleeding from esophageal varices, we have as yet insufficient controlled data to be sure that over-all survival is appreciably different in the group operated on as compared to the group not undergoing operation. Until we are convinced that operation definitely decreases mortality we feel required to allow every opportunity for the spontaneous disappearance of varices before recommending surgery.

SUMMARY

A group of 12 patients is presented. Five of these patients demonstrated the spontaneous (medical) disappearance of esophageal varices. Two demonstrated the disappearance of esophageal varices but also had inflammatory conditions of the esophagus and periesophageal tissues. The remaining five were found to have normal portal pressures at the time of surgery, despite the previous presence of esophageal varices. The theoretical background and clinical import of these findings are discussed.

SYNDROME OF HEMANGIOMA AND THROMBOCYTOPENIC PURPURA IN INFANTS

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THE PURPOSE of this report is to present two cases of infantile hemangioma associated with thrombocytopenia. Clinical observations were made correlating the thrombocytopenia with the evolution of the hemangioma. One of the patients underwent a splenectomy, while the other did not, and the value of this operative procedure for this type of thrombocytopenia will be discussed.

REPORT OF CASES

CASE 1.—R. H., a 9-month-old white boy, was admitted to Memorial Hospital on Feb. 11, 1949, with the chief complaint of a tumor mass of the right forearm, which had been present since birth.

The child was born at full term, and delivery was spontaneous. His weight at birth was 6 lb. 15 oz. (3,150 gm.).

The tumor was first noted at birth, as a slightly elevated purple mass approximately 1.5 cm. in diameter on the right upper forearm. It was said to have disappeared spontaneously at the age of 1 month, but it recurred and grew rapidly up to the time of admission.

The family history included an uneventful circumcision carried out at the age of 3 weeks without abnormal bleeding. Three weeks before admission the patient received a short course of sulfadiazine for bronchitis, which yielded to the treatment.

Physical examination on admission revealed a well-developed infant in a good state of nutrition. A café-au-lait spot was seen on the right thigh. A large bluish-pink tumor mass involving the distal part of the right arm and the upper two-thirds of the forearm was seen. The mass was 24 cm. in circumference and 10 cm. in length.

The skin of the entire body showed areas of ecchymotic discolorations. There were numerous petechiae over the trunk and extremities. There was dried blood at the nares. The head and neck were normal. Examination of heart and lungs gave normal findings. The abdomen had a normal appearance. The liver edge was palpated 3 cm. below the costal margin, and the spleen was just barely palpable.

The hemoglobin level was 8.1 gm. per 100 cc. of blood. The red blood cells amounted to 2,900,000 and the white blood corpuscles to 7,200 per cubic millimeter of blood. The differential count of white blood cells was normal. There were 72,000 platelets per cubic millimeter of blood. No clot retraction was seen after 24 hours. Bleeding time was 11 minutes, and clotting time 9 minutes. The urine was negative for sugar and albumin, and no cells were seen on microscopic examination. Examination of the bone marrow content by aspiration and smear showed some hypocellularity with slight erythroblastosis. No megakaryocytes were seen. A biopsy specimen of the tumor was diagnosed as hypertrophic hemangioma. Roentgenologic examination of the right forearm and elbow showed soft tissue enlargement, with cortical thickening of the right ulna and humerus.

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Course.—The patient received a transfusion of 120 cc. of blood on Feb. 16, and 160 cc. on Feb. 20. During this period, the platelets numbered 30,000 and 8,000 per cubic millimeter of blood. On March 16 the patient was discharged from the hospital, with no improvement in his condition. He was readmitted on April 5. In the interval between the two admissions the tumor remained unchanged but the purpuric manifestations became more intense. The platelet count was now 22,000 per cubic millimeter of blood. The hemoglobin level was 9.7 gm. per 100 cc. of blood. After administration of blood to raise the level of hemoglobin to 12.7 gm. per 100 cc., the patient underwent a splenectomy. The spleen weighed 37 gm. and measured 7 by 4 cm. Its gross appearance was not remarkable. Microscopic sections of the spleen showed some increase in phagocytosis but no other abnormal aspect. The postoperative course was uneventful. The number of platelets rose to 42,000 per cubic millimeter of blood on the first postoperative day, but the next day the number fell to 6,000 and thereafter remained between 5,000 and 18,000 until the patient was discharged on May 11, 1949. The platelet count remained under 18,000 for the six months following splenectomy. However, in June of 1950 a numeration of the platelets showed a normal value, of 216,000 per cubic millimeter of blood. At the same time there was observed a definite reduction in size of the tumor and the patient was able to use the right arm without difficulty for the first time. The number of platelets has remained normal up to the time of this report. The tumor continued to regress and has now completely disappeared.

Case 2.—A., a 3½-month-old white girl, was admitted to Memorial Hospital on Aug. 5, 1952, with the chief complaint of swelling of the left arm of four weeks' duration. The child was born at full term and delivery was spontaneous. The past and family histories were not contributory. A small bluish discoloration of the skin over the left elbow was observed at birth. This area became red four weeks before admission and began to increase in size rapidly. The patient received four injections of penicillin and other unspecified antibiotics, without beneficial results. Roentgenologic examination demonstrated an area of bone rarefaction of the head of the ulna. The patient was referred to Memorial Hospital.

Review by systems was entirely noncontributory.

Results of the physical examination were entirely normal except for the lesion of the left arm. This arm was enlarged in diameter from shoulder to wrist, with pronounced erythema and induration of the tumor mass. The color was bluish-pink. There was no adenopathy. The head and neck and the heart and lungs were normal. The abdomen had a normal appearance; the liver and spleen were not palpable.

The hemoglobin level was 8 gm. per 100 cc. of blood. The white blood cells numbered 10,600 per cubic millimeter of blood, with a normal differential count, except for the presence of four nucleated red blood cells per 100 white blood cells. The urine was negative for sugar and albumin, and microscopic examination did not show cells. From a biopsy specimen of the tumor a diagnosis of hypertrophic hemangioma was made.

Course.—Shortly after admission, purpuric lesions were observed on the skin at the site of venous puncture. Counts of the platelets were made. There were 19,000 and 3,400 platelets per cubic millimeter of blood on two successive days. Bleeding time was 9½ minutes.

Roentgenologic examination of the bones of the affected area was carried out early in the course. Periosteal elevation was diagnosed, and the possibility of osteomyelitis prompted the institution of chemotherapy. A culture of the exudate from an ulcerated area of the tumor grew a hemolytic Staphylococcus aureus. The patient received penicillin and streptomycin for three days, after which she was given chloramphenicol (Chloromycetin) for five days, the total dose being 650 mg. Examination of aspirated bone marrow at the end of the treatment with chloramphenicol demonstrated the presence of normal cellular activity and a normal number of megakaryocytes. Radiation treatment to the tumor was given for three days, representing a total dose of 300 r (air). This was given with the 120 kv. apparatus through a 2 mm. Al filter. The radiation treatment was discontinued because of the thrombocytopenia. The patient was discharged on Sept. 11, unimproved, and followed in the outpatient department. One month after discharge the platelet count was 80,000 per cubic millimeter of blood. There

was no regression in the tumor mass. In December, 1952, the tumor had definitely decreased in size and the platelet count was 200,000. When the patient was last seen, in May, 1953, the tumor had decreased 50% and the platelet count was 164,000.

The anemia of these two patients responded very well to oral iron therapy.

COMMENT

The association of thrombocytopenic purpura and hemangioma has been reported in five isolated cases in the literature.[1] In every reported case thrombocytopenia was present at the time of full development of the hemangioma, and, except in one patient who died,[1c] regression and disappearance of the tumor coincided with the return of a normal number of platelets. All the patients were infants.

The condition in the two infants described here conforms to the pattern established by previously reported cases. The hemangioma was of the hypertrophic type, and thrombocytopenia and hemorrhagic manifestations occurred when the tumor was fully developed and subsided with the regression of the tumor. Our Case 2 suggests that the return of the platelets to a normal level may precede the regression of the tumor.

From an examination of the data in these seven cases it would appear that the various treatments directed at the hemangioma were not responsible for the subsidence of the thrombocytopenia. Thus, each patient reported previously received radiation treatment. However, in Case 1 of this report no irradiation was done, and in Case 2 the patient received an insignificant amount of radiation therapy. Yet in these two patients the thrombocytopenia subsided just as rapidly as in those patients who received the roentgenologic treatment. The lack of effectiveness of splenectomy for this type of thrombocytopenia is strongly suggested by the course in our Case 1, in which thrombocytopenia was not influenced by surgical removal of the spleen. It is on the basis of this experience that splenectomy was not recommended in Case 2, and the favorable spontaneous evolution of thrombocytopenia in this patient fully justified this abstention.

The remarkable and constant correlation in all these seven patients is that between the development of the tumor and the number of platelets in the circulating blood. The thrombocytopenia was present when the tumor was fully developed, and both tumor and thrombocytopenia regressed at the same time. It appears that the number of cases observed is large enough to establish this association as a new syndrome which could be called "the thrombocytopenic purpura of hemangioma." From the observations available so far it would seem that the syndrome is seen in infants and that the prognosis of the thrombocytopenia is good. In the case reported here in which it was carried out, splenectomy was not effective as a treatment of thrombocytopenia in this syndrome, and this observation is in agree-

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ment with the observation of Bogin.[1d] Since the hemangioma has a natural tendency to regress spontaneously,[2] the association of the two components of the syndrome means that the thrombocytopenia also improves spontaneously.

It is quite probable that thrombocytopenia would be discovered in a larger proportion of cases if a platelet count were carried out for every patient. Preliminary observations, to be completed later, indicate that such is the case. Platelet counts are not usually made for patients who do not present hemorrhagic manifestations, and these may be absent with thrombocytopenia.

The question of the nature of this association between hemangioma and thrombocytopenia will require investigation. The thrombocytopenia in this syndrome is not of the type that is seen in generalized blood diseases, like aplastic anemia, for instance. Our patients had some anemia, but this was obviously due to loss of blood, as demonstrated by the normal activity of the bone marrow and the good response to iron therapy. It could be due to platelet destruction through the formation of platelet antibodies[3] related, in some obscure way, to the presence of the vascular lesion. A hypothesis that will have to be considered is that the regression of the hemangioma may be causally related to the return of a normal level of platelets in the blood. Healing of the hemangioma is usually associated with a process of thrombosis in the tumor,[2] and it is possible that a normal number of platelets is needed before healing can take place. Investigation along these lines is now in progress and will be reported later.

SUMMARY

Two cases are reported illustrating the association of thrombocytopenia with hypertrophic hemangioma in infants. It is probable that this association represents a real syndrome. Regression of the hemangioma coincided with the disappearance of thrombocytopenia. Splenectomy did not affect the thrombocytopenia in one case in which it was done.

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CLINICAL OBSERVATIONS ON THE FATTY LIVER

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CONSIDERABLE information has been accumulated on the pathogenesis,[1] anatomical changes,[2] biochemical alterations,[3] and treatment [4] of fatty liver in man and in laboratory animals. This paper will record our experiences with 102

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(Footnotes continued on next page)

patients in whom aspiration biopsy of the liver revealed fatty metamorphosis without fibrosis. Attention is directed to etiological factors, clinical and biochemical findings, response to treatment, and sequelae of the fatty liver.

MATERIALS AND METHODS

There were 77 men, 24 women, and 1 child. Ages ranged from 4 to 77 years. Eighty-six patients had consumed alcoholic beverages excessively; 21 of these were admitted for delirium tremens. In this group, 11 patients were obese, 7 had diabetes mellitus, 4 had peptic ulcer, 2 had chronic pulmonary disease, and 1 had hypertensive heart disease. Sixteen patients did not use alcohol. Four patients in this group had diabetes mellitus, four had malignant neoplasms, and 3 had cholecystitis; obesity, plumbism, inanition, carbon tetrachloride intoxication, and disseminated vascular disease each accounted for one case.

The laboratory tests used in studying these patients included determinations of serum bilirubin,[5] serum alkaline phosphatase,[6] sulfobromophthalein (Bromsulfalein) excretion,[7] serum cholesterol and esters,[8] serum albumin and globulin,[9] cephalin-cholesterol flocculation,[10] thymol turbidity,[11]

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prothrombin time,[12] and glycogen storage capacity.[13] Aspiration biopsies were performed with the Vim Silverman needle, without complication.[14] Biopsy sections were routinely fixed in formalin and the paraffin section stained with hematoxylin and eosin or the trichrome stain of Gomori.[15] For fat studies, biopsy specimens were fixed in formalin and frozen sections were stained with scarlet red and hematoxylin.[16]

Biopsy specimens with fat occupying less than 10% of the section were not included in this study (Fig. 5*A*). Thirty patients had mild fatty metamorphosis, 10 to 30% of the biopsy section consisting of fat (Fig. 5*B*); 41 patients had moderate fatty metamorphosis, 30 to 80% of the biopsy section consisting of fat (Fig. 5*C*), and 31 patients had severe fatty metamorphosis, over 80% of the biopsy section consisting of fat (Fig. 5*D*).

OBSERVATIONS

Etiological Factors.—The most marked degree of fatty liver occurred in patients whose diet consisted principally of carbohydrate, with few lipotropic-containing foods (Fig. 1). Absence of complete dietary histories, the difficult characters of

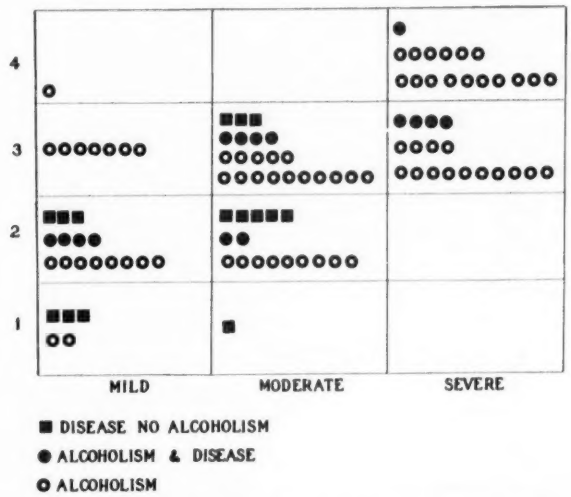

Fig. 1.—Correlation of dietary inadequacy and liver fat (the numbers 1 to 4 refer to degree of dietary deficiency observed in patients with mild, moderate, and severe fatty liver).

such studies, and lack of information about the lipotropic content of processed foods prevented precise evaluation. Caloric reduction and starvation were not associated with marked fatty changes. Six patients had normal dietary habits except for occasional irregularity (Group I); 31 patients ate well except during drinking bouts

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14. White, T. J.; Leevy, C. M.; Kemp, N. F.; Gnassi, A. M., and Price, H. P.: Needle Biopsy of the Liver: A Critical Evaluation, J. M. Soc. New Jersey **46**:549, 1949.

15. Gomori, G.: A Rapid One-Step Trichrome Stain, Am. J. Clin. Path. **20**:661, 1950.

16. Lillie, R. D.: Histopathologic Technic, Philadelphia, The Blakiston Company, 1948.

or subsequent periods of anorexia (Group II); 47 patients had diets grossly deficient in animal and vegetable protein (Group III); 18 patients had eaten only carbohydrate foods for prolonged periods (Group IV).

There was no correlation of severity of fatty metamorphosis and the amount or duration of alcoholic intake (Fig. 2). Many patients with large alcoholic intakes have normal liver structure on biopsy.[17] Estimation of alcohol consumption of patients in this series revealed 41 patients who drank alcoholic beverages in moderate quantity (Type I); 17 patients who consumed large quantities of alcoholic beverages daily but had periodic remissions (Type II); 28 patients who were chronic alcohol users, who continually consumed large quantities of whiskey, wine, or beer (Type III). Heavy alcoholic intake in patients eating only carbohydrate foods produced the severest degree of fatty metamorphosis. Fatty changes could not be related to specific types of alcoholic beverages.

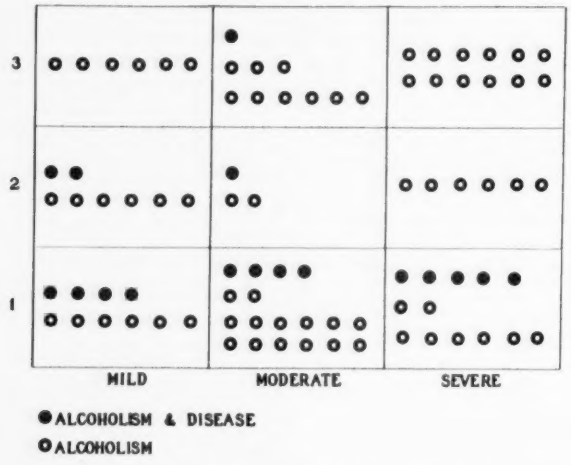

Fig. 2.—Correlation of alcoholism and liver fat (the numbers 1 to 3 refer to alcoholic patterns occurring in patients with mild, moderate, and severe fatty liver).

A correlation could not be established between the degree of liver fat and age, sex, racial background, or body type. The amount of fat in obese subjects was proportional to the excess body weight. Added factors of poor food absorption in gastrointestinal disease, glycosuria in diabetes mellitus, anoxia in heart failure, and toxemia in chemical intoxication may have contributed to development of the fatty liver.

Clinical Changes.—Clinical abnormalities were roughly proportional to the degree of liver fat and disappeared with its mobilization (Fig 3). No causal relationship could be established between fat accumulation and observed signs and symptoms. Similar clinical changes were noted in alcoholic patients with delirium tremens in whom biopsies showed normal liver or focal infiltration.[17]

17. Leevy, C. M.; Patrylo, I., and Doody, W.: Hepatic Abnormalities in Delirium Tremens, unpublished data.

Hepatomegaly was the commonest clinical sign. It was present in all except 16 patients, and in 31 instances gastrointestinal complaints were associated with it. Liver enlargement was attributed to accumulation of fat and hepatic edema, the latter possibly accounting for rapid changes in liver size in patients in whom there was only mild fatty metamorphosis. Hepatic tenderness was the second most commonly encountered physical sign. Two patients with marked fatty liver were hospitalized because of severe abdominal pain, and both internists and surgeons agreed that surgical exploration was advisable. There was no evidence of pancreatitis, gastritis, or porphyrinuria in these patients. Acute cholecystitis was simulated by right upper quadrant pain, rebound tenderness, slight fever, and leucocytosis. The operative findings suggested that pain was due to acute distention of the hepatic capsule. Histological study showed numerous fatty cysts and edema.

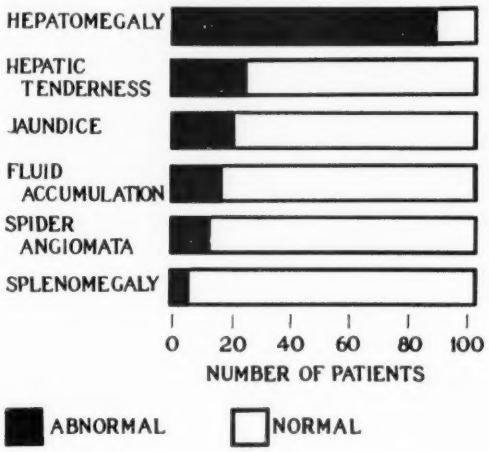

Fig. 3.—Clinical abnormalities associated with fatty liver.

The severity of jaundice was frequently unrelated to the amount of liver fat. Icterus was attributable in most instances to liver cell dysfunction. Three (9.4%) patients with mild fatty liver, 5 (12.2%) patients with moderate fatty liver, and 12 (37.5%) patients with severe fatty liver were jaundiced. In three patients whose biochemical test suggested obstructive jaundice there may have been mechanical compression of finer bile capillaries by extracellular fat. In these patients icterus gradually decreased as fat disappeared. Cholecystography after therapy showed normal visualization of the gallbladder.

Changes including spider angiomata, menstrual disturbances, impotence, and increased urinary estrogen and decreased 17-ketosteroid excretion may be related to malnutrition, since they occurred in patients with greater degrees of nutritional failure. The mechanism of splenomegaly and fluid retention was not evident. Splenomegaly was not accompanied by additional evidence of portal hypertension. The accumulation of ascites or edema was usually proportional to the amount of fat; however, several malnourished patients with little fat had peripheral edema and ascites.

Other clinical changes included delirium tremens, peripheral neuritis, and glossitis. In the group with mild fatty liver three (9.4%) patients were hospitalized with delirium tremens and two (6.3%) patients had peripheral neuritis. In the group with moderate fatty liver 10 (24.4%) patients had delirium tremens; none of these patients had peripheral neuritis. In the group with severe fatty liver eight (25.0%) patients had delirium tremens and six (18.7%) patients had peripheral neuritis.

A fasting blood sugar level over 130 mg. per 100 cc. was present in 19 patients (Fig. 4). Eleven of these patients had diabetes mellitus with secondary fatty liver changes.[18] In eight patients hyperglycemia and glycosuria disappeared when fat was mobilized.[19] Two patients had hypoglycemia, one with a blood sugar level of 35 mg.,

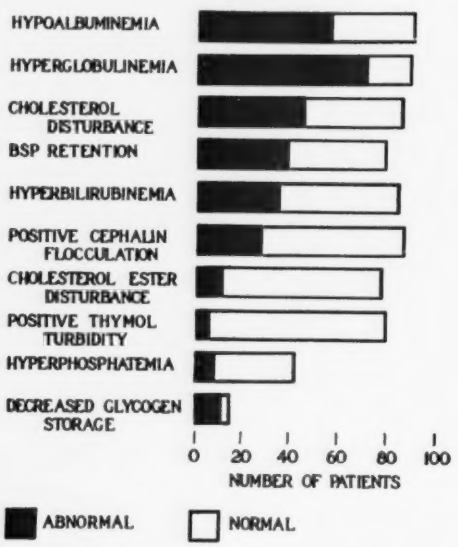

Fig. 4.—Laboratory abnormalities associated with fatty liver.

and the other 60 mg. per 100 cc. Both patients were semicomatose on admission and required intravenous dextrose for restoration of consciousness.

A red blood cell count less than 4,000,000 was present in 37 patients. There were 7 patients with macrocytic hyperchromic anemia, 16 patients with normocytic normochromic anemia, and 1 patient with microcytic hypochromic anemia. Blood loss was responsible in four of the patients with normocytic anemia. The anemia in other patients was not further classified and improved with treatment.

Urinalysis on admission revealed albuminuria in 54.9% of the patients. This was accompanied by casts in many instances and by transient slight elevations of

18. Leevy, C. M.; Ryan, C. M., and Fineberg, J. C.: Diabetes Mellitus and Liver Dysfunction: Etiologic and Therapeutic Considerations, Am. J. Med. **8**:290, 1950.

19. Leevy, C. M.; Fineberg, J. C.; White, T. J., and Gnassi, A. M.: Hyperglycemia and Glycosuria in the Chronic Alcoholic with Hepatic Insufficiency, Am. J. Med. Sc. **223**:88, 1952.

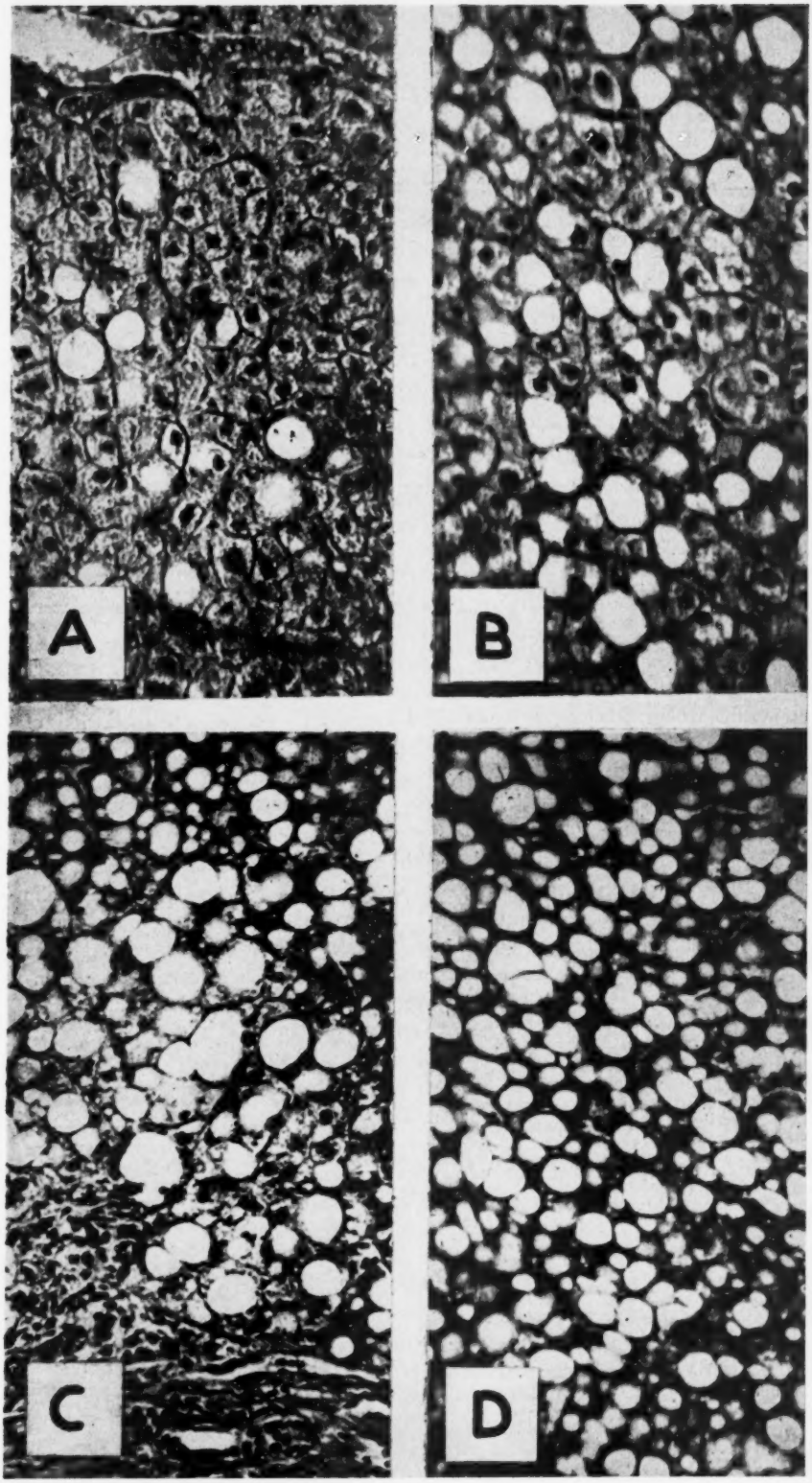

Fig. 5.—Classifications of fatty liver: *A*, fat occupying less than 10% of biopsy section; *B*, mild fatty liver; *C*, moderate fatty liver; *D*, severe fatty liver.

nonprotein nitrogen levels in 18 patients. Although the renal abnormalities disappeared with mobilization of fat, no interrelationship between fat and urinary changes could be established. Similar degrees of albuminuria were noted in patients with chronic alcoholism and normal liver histology. Urinary abnormalities disappeared with diet and rest. Addis counts, results of renal function studies, and findings on needle biopsy of the kidney were normal in three patients studied.

Biochemical Liver Function Changes.—There was no correlation between the amount of liver fat and biochemical liver function tests. Abnormal results of these tests could often be correlated with clinical evidence of malnutrition. Patients with chronic alcoholism and fatty liver had findings similar to those with normal histology or focal infiltration.[17] Biochemical tests performed after elimination of fat occasionally showed persistent abnormalities which necessitated further treatment.

The most frequent biochemical abnormality was an alteration in plasma protein (Fig. 4). There was no correlation between the amount of fat accumulation and the degree of protein change. The most consistent index of severe fatty infiltration was the sulfobromophthalein test. Sulfobromophthalein retention ranged to 30% in many patients without complicating diseases. Higher levels of retention were associated with anemia and fluid retention.

Elevated serum bilirubin values usually ranged between 1.0 and 5.0 mg. per 100 cc. Except for three patients with marked bilirubin retention and high "one-minute" bilirubin levels, the hyperbilirubinemia was due to a combination of direct- and indirect-reacting bilirubin. Hypercholesterolemia was present in many patients without impairment of bilirubin excretion or elevation of serum alkaline phosphatase. Abnormal prothrombin time and poor glycogen storage were frequently expressions of deficient vitamin K and carbohydrate intake, respectively.

Histologic Studies.—Biopsies revealed intracellular and extracellular fat in each patient. There was occasional pleomorphism and lymphocytic infiltration. Hyalin or ceroid was not found in any specimen. There was no correlation between clinical and biochemical abnormalities and the localization of fat. Morphological studies confirmed Hartroft's observations in animals.[2a] With fat stains one could demonstrate conglobation of intracellular fat (Fig. 6*A*); development of large fat globules which displace the liver cell nucleus (Fig. 6*B*) and merged to form fatty cysts (Fig. 6*C*), and rupture of fatty cysts, producing an inflammatory reaction which consisted of lymphocytes and an exudate (Fig. 6*D*).

Intracellular fat was mobilized within a period of three weeks. Elimination of extracellular fat required four to six weeks. A decrease in size of fatty cysts was associated with deposition of intracellular lipid in their walls.[2c] After treatment, cells in the cyst walls resumed the appearance of normal parenchyma. Focal areas of lymphocytic infiltration often remained in biopsy sections after fat was mobilized.

Repeat biopsies in two patients after intervals of alcoholism and poor dietary intake showed an ingrowth of collagen fibers. Connective tissue appeared in the central and portal areas and was associated with an inflammatory reaction (Fig. 7*A*). Subsequent biopsy in one of these patients revealed typical portal cirrhosis with periportal fibrosis and pseudolobulation (Fig. 7*B*). Repeat biopsy studies in seven patients with fatty liver who continued to eat poorly and consume large

quantities of whiskey showed portal cirrhosis one and one-half to five years after initial study. The cirrhosis was accompanied by hyaline necrosis in one instance (Fig. 7*C*) and fatty changes in five instances (Fig. 7*D*).

The sequence of fatty liver, development of fatty cysts with rupture, round cell inflammation with exudation, ingrowth of fibrous connective tissue, and regeneration of liver cells seemed applicable to those patients in whom cirrhosis developed. No objective relationship could be established between rupture of fatty cysts and liver

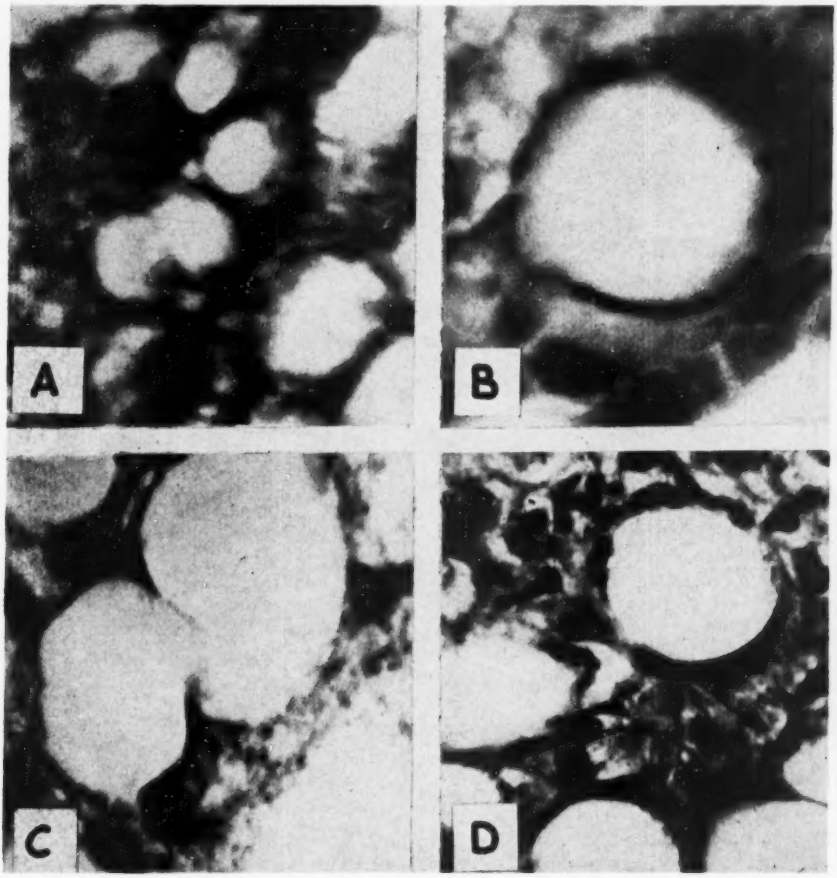

Fig. 6.—Evolution of fatty cysts: *A*, conglobation of intracellular fat globules; *B*, large fat globule displacing liver cell nucleus; *C*, rupture of fatty globules to form fatty cysts; *D*, rupture of fatty cysts with surrounding inflammatory reaction.

cell regeneration or the development of fibrous connective tissue. Neither proliferation of reticulum cells,[3b] fibroblastic transformation of mesenchymal cells,[20] nor

20. Moschowitz, E.: Laennec Cirrhosis: Its Histogenesis, with Special Reference to the Role of Angiogenesis, Arch. Path. **45**:187, 1948. Porter, K. R.: Repair Processes in Connective Tissues, in Transactions of the Second Conference on Connective Tissues, May 24-25, 1951, edited by C. Ragen, New York, Josiah Macy, Jr. Foundation, 1952.

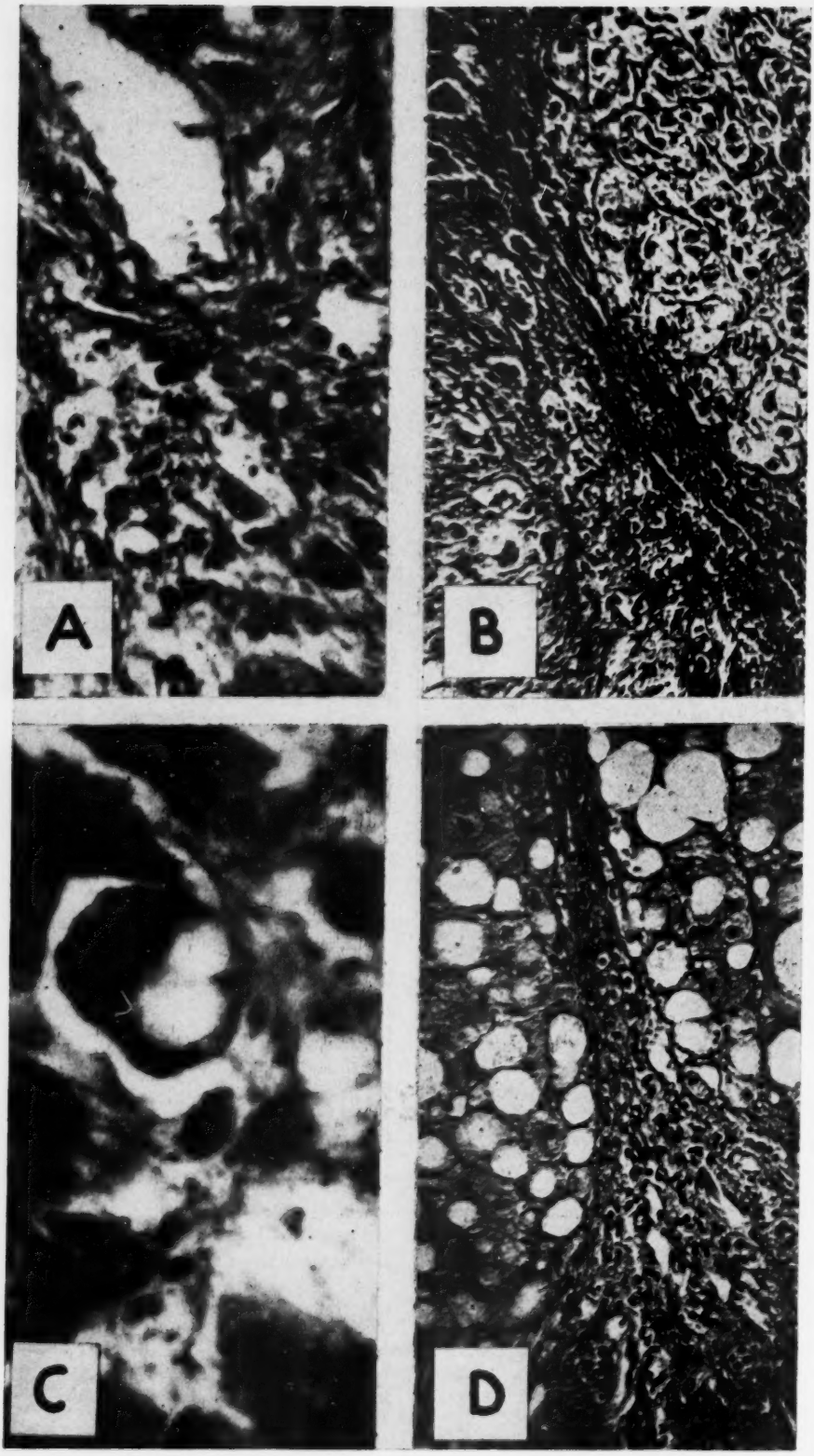

Fig. 7.—Transition of fatty liver to portal cirrhosis: *A*, appearance of connective tissue in fatty liver; *B*, portal cirrhosis two years later; *C*, hyaline necrosis in portal cirrhosis; *D*, fatty changes in portal cirrhosis.

serous exudation,[21] postulated as responsible for liver fibrosis, could be demonstrated. A preliminary long-term study of chronic alcoholics with normal liver at the time of original observation has not revealed the development of cirrhosis.[17]

Therapeutic Studies.—Pilot studies demonstrated that bed rest and a diet containing adequate amounts of protein and lipotropic substances could transform a severe fatty liver to a normal liver within a six-week period. The general hospital diet; a high carbohydrate, high protein, low fat diet, and a high carbohydrate, high protein, high fat diet all provided similar results.

A series of clinical experiments was instituted by Dr. Norman Deane of our clinic in 1948 to test the capacity of various drugs to accelerate the removal of fat. Serial clinical, biochemical, and histological studies were performed to determine the rate of fat disappearance. The relative merit of a therapeutic regimen was evaluated by determining the amount of fat present in biopsy specimens at the end of a 30-day period. To date, 21 patients with severe fatty metamorphosis of the liver have thus been studied. Each of the patients was at rest in bed, and the diet consisted of 350 gm. of carbohydrate, 125 gm. of protein, and 100 gm. of fat. Four patients received no supplements. Five patients received multivitamin preparations, containing 75,000 units of vitamin A, 3,000 units of vitamin D, 30 mg. of thiamine hydrochloride, 15 mg. of riboflavin, 450 mg. of nicotinic acid (niacin), and 450 mg. of ascorbic acid daily. Five patients received multivitamin preparations and 6 gm. each of methionine and choline daily; four patients received 120 γ of cyanocobalamin (vitamin B_{12}) daily; one patient received 5 cc. of lipoadrenal extract each day; two patients received 50 mg. of cortisone each day.

TABLE 1.—*Effect of Various Therapeutic Regimens on Mobilization of Liver Fat*

Regimen	Patients, No.	Fat in 4 Wk.			Fat in 6 Wk.		
		None	0-10% Fat	Over 10% Fat	None	0-10% Fat	Over 10% Fat
Rest and diet	4	2	2	0	3	1	0
Rest, diet, and multivitamins	5	1	3	1	4	1	0
Rest, diet, vitamins, and lipotropes	5	2	3	0	3	2	0
Rest, diet, and cyanocobalamin	4	2	1	1	3	1	0
Rest, diet, and adrenal steroids	3	1	1	1	2	1	0

Multivitamin preparations, choline and methionine, cyanocobalamin, or adrenal steroids added to rest and diet did not shorten the time period required for the removal of liver fat. With each regimen, some patients showed slight fat on biopsy at the end of 30 days. At the end of six weeks, none of the patients had significant amounts of fat on biopsy (Table 1). The time period of four to six weeks required for removal of fat in patients with severe fatty metamorphosis suggests that time is as essential as the quantity of lipotropic substances.

Lipotropic agents were shown to be important in patients with anorexia or systemic disease interfering with normal nutrition. Five patients with fatty liver who failed to eat an adequate diet had little change in the amount of liver fat until lipotropic substances were added. Cyanocobalamin was most useful in this group, as it could be given parenterally. Two patients with severe fatty liver who resumed

21. Hill, K. R.; Rhodes, K.; Stafford, J. L., and Aub, R.: Serous Hepatosis: A Pathogenesis of Hepatic Fibrosis in Jamaican Children, Brit. Med. J. **1**:117, 1953.

TABLE 2.—*Effect of Continued Poor Dietary Intake and Alcoholism on Histology*

Patient	Time of Study*	Interval of Study, Yr.	Fibrosis	Fat	Pleomorphism	Bile Duct Proliferation	Pseudolobulation	Infiltration: Lymphocytes	Infiltration: Polymorphonuclears	Pathological Diagnosis
L. B.	A	4	0	3+	2+	1+	0	2+	1+	Fatty liver
	B		2+	0	3+	3+	2+	2+	1+	Portal cirrhosis
J. B.	A	4½	0	4+	1+	0	0	1+	0	Fatty liver
	B		3+	1+	4+	3+	3+	3+	1+	Portal cirrhosis
L. D.	A	4½	0	3+	1+	1+	0	2+	1+	Fatty liver
	B		3+	1+	3+	3+	2+	3+	1+	Portal cirrhosis
W. M.	A	4	0	3+	1+	0	0	1+	0	Fatty liver
	B		3+	2+	3+	2+	2+	3+	1+	Portal cirrhosis
T. McC.	A	4½	0	4+	1+	0	0	1+	0	Fatty liver
	B		1+	3+	3+	1+	2+	3+	1+	Portal cirrhosis
J. S.	A	3½	0	2+	0	0	0	1+	0	Fatty liver
	B		1+	2+	3+	2+	1+	1+	0	Portal cirrhosis
E. W.	A	1½	0	4+	2+	0	0	2+	1+	Fatty liver
	B		1+	0	2+	2+	1+	2+	1+	Portal cirrhosis
M. A.	A	4	0	4+	1+	0	0	1+	0	Fatty liver
	B		1+	1+	1+	1+	0	2+	0	Fatty liver with fibrosis
J. C.	A	4½	0	2+	1+	0	0	1+	0	Fatty liver
	B		1+	2+	2+	0	0	1+	0	Periportal fibrosis
F. D.	A	4	0	2+	1+	0	0	1+	0	Fatty liver
	B		0	2+	2+	1+	0	1+	0	Fatty liver
W. F.	A	5	0	3+	2+	0	0	1+	0	Fatty liver
	B		0	3+	2+	0	0	1+	0	Fatty liver

* A indicates original study; B, restudy.

TABLE 3.—*Effect of Continued Poor Dietary Intake and Alcoholism on Biochemical Changes*

Patient	Time of Study*	Interval of Study, Yr.	Bil.,† Mg./100 Cc.	BSP,† %	Chol.,† Mg./100 Cc.	Chol. Est.,† Mg./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Cephalin Flocc.
L. B.	A	4	0.3	6.0	171	82	3.1	3.1	1+
	B		2.2	32.0	138	79	2.5	5.0	2+
J. B.	A	4½	1.8	0	232	77	2.4	4.4	Neg.
	B		0.5	0	143	79	3.4	3.4	3+
L. D.	A	4½	2.2	9.0	294	198	4.1	3.4	2+
	B		1.2	0.0	325	176	3.09	3.71	2+
W. M.	A	4	0.7	0	239	130	2.24	3.96	Neg.
	B		0.5	16.5	283	167	2.9	4.6	3+
T. McC.	A	4½	2.2	7.0	146	95	2.88	3.92	Neg.
	B		1.0	7.5	246	116	3.3	4.9	2+
J. S.	A	3½	3.6	0	343	110	3.64	3.16	Neg.
	B		0.0	0	280	96	3.6	4.6	2+
E. W.	A	1½	5.2	27.0	595	316	2.81	3.99	Neg.
	B		1.0	5.0	308	167	3.0	4.2	2+
M. A.	A	4	1.6	0	362	...	2.92	3.88	2+
	B		0	7	299	199	3.1	3.4	1+
J. C.	A	4½	0.5	30.0	...	...	3.66	3.84	1+
	B		0.5	5.0	253	149	2.8	4.7	3+
F. D.	A	4	0	0	246	141	3.96	2.84	Neg.
	B		0.7	0	...	...	2.3	5.2	1+
W. F.	A	5	0.5	23.0	232	114	4.4	3.8	....
	B		0.5	23.0	246	...	3.2	4.0	Neg.

* A, original study; B, restudy.
† Bil., bilirubin; BSP, sulfobromophthalein retention; Chol., cholesterol; Chol. Est., cholesterol esters.

moderate activity while maintaining an adequate diet had a disappearance of liver fat in a six-week period, suggesting that complete rest may not be necessary. Fatty liver due to chemical intoxication responded less rapidly to therapy.

Sequelae.—Twenty patients with fatty liver due to poor dietary intakes and alcoholism had serial clinical, biochemical, and histological studies one and one-half to five years after their initial observation. Examination of nine patients who maintained a good dietary intake and discontinued the use of alcohol revealed no clinical, biochemical, or histological evidence of liver disease. Evaluation of 11 patients who continued the use of alcohol and ate poorly revealed hepatic abnormalities in each instance. Repeat biopsies showed portal cirrhosis in seven patients, fatty liver with beginning fibrosis in two patients, and fatty liver without fibrosis in two patients (Table 2).

Clinical study of the patients in whom portal cirrhosis developed revealed an increase in hepatomegaly in six patients and a decrease in five patients. Splenomegaly appeared in three patients, fluid retention in three patients, and jaundice in one patient. In a patient with a familial history of diabetes mellitus hyperglycemia and glycosuria developed, and in a hypertensive patient congestive heart failure developed. Portal cirrhosis was associated with a macrocytic hemolytic anemia in one patient.

Biochemical liver function tests were of considerable interest, as there were no consistent differences in the patterns observed with a fatty liver and portal cirrhosis (Table 3). In several patients serum bilirubin and sulfobromophthalein excretion were less abnormal after development of portal cirrhosis. Cholesterol and protein partition studies varied; the cephalin flocculation became more abnormal in six patients.

A diagnosis of portal cirrhosis was based on the presence of periportal fibrosis, bile duct proliferation, and pseudolobulation, with or without fatty or lymphocytic infiltration. Histologic studies showed mild degrees of cirrhosis in each of the patients. The fibrous connective tissue appeared young and was associated with pleomorphism and lymphocytic infiltration.

Of the two patients with consistent fat Korsakoff's psychosis developed in one, necessitating institutional custody. There were no other clinical changes. Biochemical study showed progressive decrease in serum albumin in one patient. No clinical alterations were noted in the patient with fat and fibrosis. Biochemical patterns also remained unaltered.

COMMENT

The incidence of fatty liver will vary with the population studied. This group represented 7.8% of 1,300 aspiration biopsies performed in the Jersey City Medical Center. An occasional fat droplet in stainable form may normally occur in the human liver. The liver may show considerable fat histologically, while chemical analysis of total liver lipids may reveal only slight abnormalities. In most instances, however, there is a good correlation between morphological and chemical analysis of liver fat. Total lipids in the mild fatty liver range between 8 and 14% of total liver weight, for a moderate fatty liver between 14 and 25% of total liver weight, and for a severe fatty liver between 25 and 40% of total liver weight.[8a,b]

Lipotropic substances are necessary for transport or oxidation [1] of fat and must be supplied to prevent its accumulation in the liver. The relationship of fatty liver to deficiency of lipotropic substance or substances has been established in animals.[1b] Radioactive phosphorous studies suggest that this relationship is also true for man.[1d] An absolute deficiency may result from a lack of intake; a relative deficiency occurs with increased demands. Alcohol, thiamine hydrochloride, and high carbohydrate intakes increase the need for lipotropic substances. Most patients in this series had a dietary abnormality which resulted in a lipotropic deficiency. It was accentuated by alcoholism in many instances. Malnutrition caused fatty liver only if there was a relative deficiency of fat-removing agents.

Alcoholic patients with normal, fatty, or cirrhotic livers may have identical clinical and biochemical abnormalities. Histological studies are necessary for diagnosis. Use of a composite approach including clinical, etiological, biochemical, and histological studies is essential for proper therapeutic perspective. Although excess liver fat may represent a specific type of nutritional deficiency, it is frequently accompanied by other evidence of malnutrition. Because of the complete reversibility of this condition, study of the fatty liver provides an excellent medium for observing the interrelations of clinical and laboratory alterations in liver disease. Further study is required to determine the histochemical processes involved in the transformation of the fatty liver into a cirrhotic process.

Since the fatty liver is curable, it is essential that it be recognized and treated as soon as possible, to forestall the development of a fibrotic liver and its consequences. In prophylaxis rehabilitation of the alcoholic patient is of prime importance. Maintenance of an adequate intake of lipotropic substances is required to prevent chronic liver injury in dibetes mellitus,[22] ulcerative colitis,[23] heart failure,[24] and other systemic diseases. Weight reduction is essential for obese patients.[25]

SUMMARY AND CONCLUSIONS

Study was made of 102 patients in whom aspiration liver biopsy revealed fatty metamorphosis without fibrosis, to establish the significance of the fatty liver. Thirty patients had mild fatty liver, 41 patients had moderate fatty liver, and 31 patients had severe fatty liver.

The fatty liver is related to relative deficiency of lipotropic substances. Poor nutritional states due to obesity, inanition, and systemic disease showed fatty liver changes similar to those seen in alcoholism. The extent of fat deposition was roughly proportional to the lack of lipotropic substances. The amount, duration, and type of alcohol ingestion showed no correlation.

Aspiration liver biopsy provided the most certain approach to diagnosis. Clinical changes such as hepatomegaly, icterus, fluid accumulation, anemia, hyperglycemia,

22. Connor, C. L.: Fatty Infiltration of the Liver and the Development of Cirrhosis in Diabetics and Chronic Alcoholism, Am. J. Path. **14**:347, 1938. Leevy, Ryan, and Fineberg.[18]

23. Kleckner, M. S.; Stauffer, M. H.; Bargen, J. A., and Dockerty, M. D.: Hepatic Lesions in the Living Patient with Chronic Ulcerative Colitis as Demonstrated by Needle Biopsy, Gastroenterology **22**:13, 1952.

24. White, T. J.; Wallace, R. B.; Gnassi, A. M.; Kemp, N. F.; Price, P., and Leevy, C. M.: Hepatic Abnormalities in Congestive Heart Failure: Needle Biopsy Studies, Circulation **3**:501, 1951.

25 Zelman, S.: The Liver in Obesity, A. M. A. Arch. Int. Med. **90**:141, 1952.

hypoglycemia, urinary abnormalities, and biochemical liver dysfunction improved with mobilization of fat. These abnormalities as well as excess liver fat appeared to reflect nutritional disturbances.

Rest and an adequate diet were curative for most patients with fatty liver. Supplementary measures, such as use of multivitamin preparations, choline, methionine, cyanocobalamin (vitamin B_{12}), and adrenal steroids, did not shorten the time required for the removal of liver fat. Their chief value was for patients with anorexia or complicating diseases which interfered with normal food intake.

Serial biopsy studies demonstrated the development of fatty cysts with rupture, round cell inflammation with an exudative reaction, and an ingrowth of fibrous connective tissue. Portal cirrhosis developed in seven patients who continued to ingest alcohol while on a poor diet. Early recognition of the fatty liver and effective rehabilitation of the patient prevent this complication.

Alcoholic patients should be evaluated periodically for the presence of fatty liver and intensive treatment given if it is found. Constant attention to lipotropic intake is desirable for patients with diseases which interfere with normal dietary habits.

DIABETES INSIPIDUS IN PREGNANCY

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DIABETES insipidus is a rare complication of pregnancy. When this disease does happen to be associated with the pregnant state, however, considerable interest attaches to the combination, since there are implications both from the obstetrical and from the endocrine standpoint. To the obstetrician it is of importance to know whether an insufficient production of oxytocic hormone coincides with the inadequate elaboration of antidiuretic hormone, with the resultant possibility of dystocia. The obstetrician is interested also in the possibility that posterior pituitary extract administration, necessary for the treatment of the diabetes insipidus, might be responsible for the induction of premature labor. From an endocrine standpoint, further information is needed concerning the effect various normal hormonal shifts during pregnancy might have upon the function of the posterior lobe of the pituitary gland. That such shifts might well have an important effect is suggested by the well-known fact that in diabetes insipidus the function of other endocrine glands has a very important bearing upon the course of the disease.

For these reasons it is considered important that all cases of diabetes insipidus associated with pregnancy should be studied in detail and the findings made available in the literature, so that, in time, a sufficient accumulation of data may be available to allow definite conclusions to be drawn. The first case herein reported is the only one, to our knowledge, in which the diagnosis of diabetes insipidus during pregnancy has been confirmed by the Hare test [1]; the second, in which the diagnosis was made by this test prior to pregnancy, was studied by means of another technique. The latter involves the measurement of the solute concentration of urine and plasma (urine: plasma ratio) during a three-hour period of fluid restriction.[2] Both of these tests make possible the distinction between psychogenic polydipsia, an example of which is included in this report, and true diabetes insipidus.

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1. Hickey, R. C., and Hare, K.: The Renal Excretion of Chloride and Water in Diabetes Insipidus, J. Clin. Invest. **23**:768-775, 1944.

2. Frank, M. N.; Dreifus, L. S., and Bellet, S.: Personal communication to the authors.

REPORT OF CASES

CASE 1.—A 35-year-old Negro woman had had her last menstrual period on Feb. 13, 1950. Other than the usual symptoms of pregnancy she had had no complaints until approximately the sixth month, when she began to experience polydipsia and polyuria which increased rapidly to the point of great annoyance to the patient, including considerable interference with her rest at night. She was admitted to the Philadelphia General Hospital on Oct. 19, 1950, stating that she would "rather have water than food," and estimating that her water intake was approximately a quart (0.95 liter) per hour. During a previous pregnancy, which resulted in delivery of a normal child in August 1949, she had had increased thirst beginning about the sixth month and disappearing at delivery, but it was not increased to the extent experienced during the present pregnancy. The remainder of the history was noncontributory.

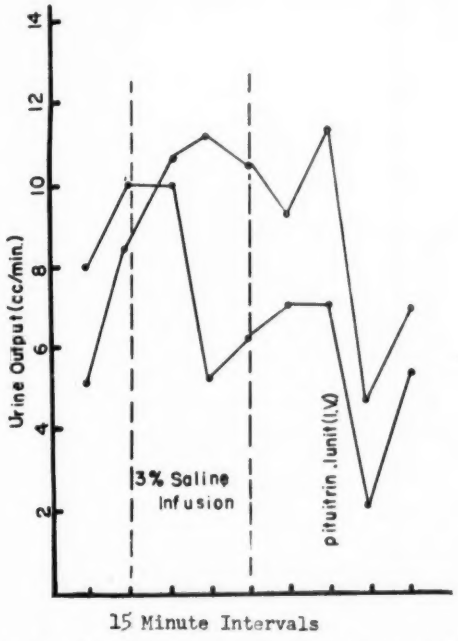

Fig. 1 (Case 1).—Hare tests prior to delivery, indicative of diabetes insipidus.

Examination showed a Negro woman of short stature who was estimated to be eight months pregnant. Apart from the pregnancy, careful examination revealed no significant findings.

The serological tests for syphilis were negative. The urine was normal except for a specific gravity of 1.002. There was no anemia or other abnormality evident upon complete blood cell count. The blood sugar was 67 gm., the blood urea nitrogen 5 mg., the serum calcium 9.34 mg., the chlorides 683 mg., and the blood cholesterol 284 mg. per 100 cc., with 66% esters. The hematocrit level was 38 vol.%. Total blood protein was 7.9 gm., albumin 4.9 gm., and globulin 3.0 gm. per 100 cc.

The skull showed no abnormality on roentgen examination. An abdominal film showed a single fetus, with head presentation. There was no evidence of calcification in the renal areas. The chest was normal on photofluorographic examination.

During her hospital stay the patient continued to consume large quantities of water. Her urine output was also greatly increased. The mean fluid intake prior to delivery was 11,500 cc. daily, ranging from 7,500 to 14,500 cc.; the mean urinary output was 9,500 cc. daily, ranging from 6,500 to 13,900 cc.

On Nov. 11, 1950, the patient went into spontaneous labor. After 17 hours of what was thought to be normal labor the patient delivered a 7 lb. (3,150 gm.) living girl on Nov. 12, 1950. The patient was given ergonovine (Ergotrate) but no posterior pituitary (Pituitrin) during labor. Following delivery the mean fluid intake decreased promptly to 4,000 cc. daily, ranging from 3,300 to 4,800 cc.; during this period, the mean urine output was 2,650 cc. daily, ranging from 2,000 to 3,000 cc.

The patient noted that after labor her desire for water had decreased to normal and her urine output had diminished to normal. A Hare test performed six days after delivery was found to be normal, as shown in Figure 2. The patient was discharged and has been followed in the outpatient department. There are no signs of diabetes insipidus in the infant.

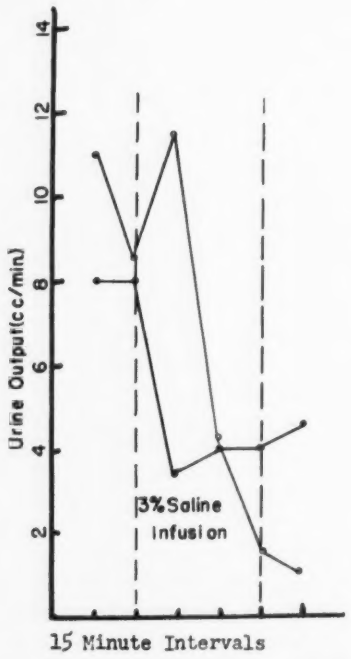

Fig. 2 (Case 1).—Hare tests after delivery, showing normal response.

Case 2.—A. T., age 15 years, was admitted to the Temple University Hospital on Jan. 18, 1951, for study as to the cause of excessive fluid intake and urination present since the age of 3 months. She had occasionally experienced suprapubic discomfort presumably due to distension of the urinary bladder, but no other symptoms were noted in the history or review of symptoms. The past medical history disclosed that she had been studied briefly at the age of 7 years, at another hospital, for enuresis and had been given injections without benefit. Her birth record was normal; she was a full-term infant delivered without instrumentation and remained well except for the large fluid intake and output, which developed during infancy, and enuresis persisting until she was 9 years of age. Her growth and development were normal, with menarche occurring at the age of 15 years, followed by normal regular menstruation. Physical examination showed no abnormality; the blood pressure was 115/75. There were no abnormal neurological findings.

During her hospitalization the patient consumed between 10,250 and 19,000 cc. of fluid (mean 15,500 cc.) and eliminated from 8,000 to 17,500 cc. of urine (mean 11,800 cc.) daily. When

given vasopressin (Pitressin) tannate in oil, 2 cc. daily, by injection, the fluid intake varied from 4,500 to 9,000 cc. (mean 7,500 cc.), with urine output from 3,000 to 6,500 cc. (mean 4,800 cc.). The nasal insufflation of posterior pituitary powder daily proved equally effective in reducing the urine volume and thirst. The specific gravity of the urine ranged from 1.000 to 0.003 throughout the period of study.

Laboratory studies revealed a slightly hypochromic anemia, with hemoglobin 10.0 gm. and red cell count 3,370,000; the white cell and differential counts were normal. The blood sugar was 90 mg. per 100 cc.; the blood urea nitrogen was 9 mg. per 100 cc. The serum chlorides, sodium, and potassium were determined repeatedly and were found to be normal: chloride 101

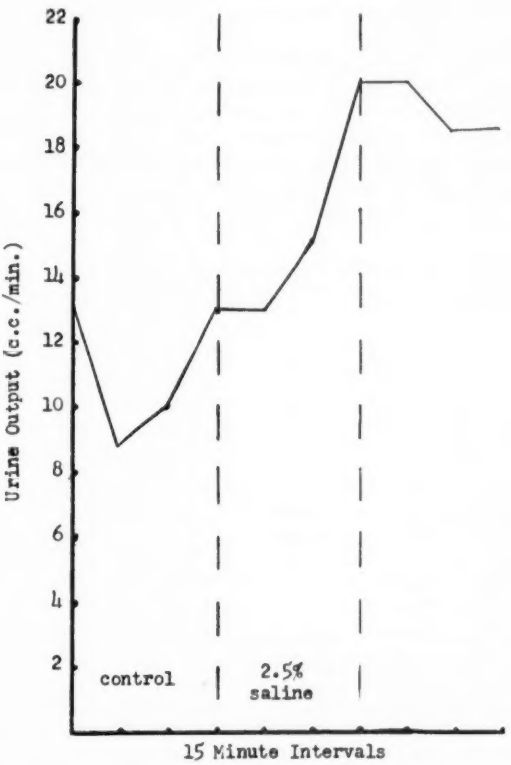

Fig. 3 (Case 2).—Hare test prior to pregnancy indicative of diabetes insipidus.

to 104 mEq., sodium 132 to 138 mEq., and potassium 3.65 to 4.0 mEq. The serum calcium was 11.5 mg. per 100 cc. The cholesterol was 216 mg. per 100 cc., with 44% esterification. The 24-hour urinary 17-ketosteroid levels ranged from 3.3 mg. to 20.4 mg.; the 11-oxysteroids (reducing) were 4.3 mg. and 4.0 mg. The serum total protein was 6.0 gm. per 100 cc., with 3.9 gm. of albumin and 2.1 gm. of globulin. The basal metabolism rate was — 16. X-rays of skull, chest, and abdomen showed no abnormalities. The eosinophile response to corticotropin (ACTH) and the decrease in fluorescein spread with hyaluronidase after corticotropin gave evidence of normal adrenal cortex function. An intravenous pyelogram revealed no significant abnormalities.

On Jan. 23, 1951, prior to any treatment, the hypertonic saline test was performed. The results of this study are recorded in Figure 3. Unfortunately, the administration of vasopressin at the conclusion of the test was omitted; however, subsequent therapy with this agent markedly reduced the fluid intake and output.

The patient was dismissed from the hospital on Feb. 22, 1951, receiving nasal insufflation therapy of posterior pituitary powder daily. Five days after she returned home, intense urticaria of the face and swelling of the joints of fingers, wrists, elbows, knees, ankles, and feet, with associated arthralgia, developed. Skin testing with all available posterior pituitary preparations revealed sensitivity only to that being used intranasally. On this basis, the diagnosis of allergic reaction to the posterior pituitary hormone was made, resulting in cessation of treatment for several months. The patient was then given a therapeutic trial of the sublingual administration of posterior pituitary tablets, 5 units three times daily, which was well tolerated but ineffective in controlling polyuria.

In August 1952 the patient complained again of lower abdominal pain and of absent menses of three months' duration. The symptoms of diabetes insipidus had persisted. Physical examination revealed a suprapubic mass, which, by pelvic examination, was determined to be the uterus enlarged to the size of 12 to 14 weeks' gestation. The catheterized urine specimen was normal; the serological tests for syphilis were negative. The hemoglobin was again 9.6 gm.

During the next two months the patient received iron and vitamin therapy but no posterior pituitary preparations. However, there was no response in the hemoglobin values, and she was

TABLE 1.—*Effect of Fluid Restriction on Serum and Urine Solute Concentration*

	Blood			Urine		
Time after Fluid Restriction	Na+, mEq./L.	K+, mEq./L.	Osmotic Pressure, Mosm./L.	Na, mEq./L.	K, mEq./L.	Osmotic Pressure Mosm./L.
2 hr.	142	5.58	314	17.0	6.8	97
3 hr.	147	4.26	312	9.9	8.0	117

readmitted to the hospital on Oct. 31, 1952, because of excessive weight gain, ankle edema, and sporadic vomiting. The blood pressure was 110/70. The fluid intake continued to range between 9 and 16 liters (mean 12.5 liters), and urine output was between 8 and 15.3 liters (mean 10.8 liters) daily. The 17-ketosteroids on this admission were 4.6 per 24 hours. The hemoglobin was raised to 11.6 gm. by blood transfusion. A skin test performed with aqueous vasopressin was normal.

Osmotic pressure measurements were performed on serum and urine with the freezing-point-lowering method [2] during the patient's pregnancy at a time when no vasopressin therapy was being employed. In normal subjects, after fluids have been withheld for three hours, the urine should be concentrated so that the osmotic pressure will exceed that of the blood.[2] The failure of the urine solute concentration and osmotic pressure to increase demonstrates the inability of the distal tubules to elaborate urine hypertonic to the blood and is consistent with the findings in diabetes insipidus.

Following the patient's discharge from the hospital, vasopressin tannate in oil, 2 cc. daily, failed to control the symptoms of polyuria; however, she was unable to measure the urine volume accurately, because of marked urinary frequency.

Her final admission to the hospital was arranged shortly before term. At this time there were no significant complications, and a spontaneous delivery of a stillborn fetus occurred on Feb. 26, 1953. Autopsy performed upon the infant, who weighed 8 lb. (3,630 gm.), revealed generalized edema and cerebral edema. The patients postpartum course was uneventful except that polyuria and polydipsia persisted. The fluid intake ranged from 8 to 12 liters and the urine output from 6 to 11 liters until the time of her dismissal from the hospital, on March 4, 1953. She has been followed in the outpatient department since delivery, where the persistence of an excessive fluid intake and output has been noted. Vasopressin tannate injections have been taken very irregularly by the patient.

COMMENT

Incidence of Diabetes Insipidus in Pregnancy and Chronological Relationship.—The exact incidence of diabetes insipidus in pregnancy cannot be estimated with accuracy. Reports in the literature are conflicting. Some of the available figures are summarized in Table 2.[3]

The cases in this table cannot be totaled, since, undoubtedly, the same cases are included in several different reports. DeLee [4] states that the incidence of diabetes insipidus in pregnancy is 3 in 50,000. Inasmuch as this is the incidence of diabetes insipidus in general, one would suspect that the incidence of diabetes insipidus during pregnancy is the same as in the general population of patients.

According to Blotner [3d] there are six possible chronological relationships of diabetes insipidus and pregnancy, granting that the various cases reported in the literature in which the Hare test was not done are all actually cases of diabetes insipidus. First, preexisting diabetes insipidus may be aggravated by pregnancy.[3b,d] Secondly, diabetes insipidus may appear transiently only during pregnancy, as in our first case.[5] Novak's case is of particular interest in this respect, since the symptoms of the disease were present during each of 10 pregnancies and absent during

TABLE 2.—*Incidence of Diabetes Insipidus in Pregnancy*

Author	Year	Old Cases Recorded	New Cases
Soule, S. D.[3a]	1937	36	1
Greene, J. A.[3b]	1939	..	1
Carter, P. J.[3c]	1940	26	1
Blotner, H.[3d]	1942	..	3
Lake, E. M.[3e]	1947	27	1

the nonpregnant intervals. Thirdly, a case has been reported [5a] in which preexisting diabetes insipidus was ameliorated during pregnancy. Fourthly, several cases [6] have been reported in which diabetes insipidus antedating pregnancy has been uninfluenced by the gravid state, as in our second patient. Fifthly, diabetes insipidus may appear during pregnancy and persist after pregnancy. Along this line French [7] believes that the "mental shock" of pregnancy may precipitate diabetes insipidus

3. (*a*) Soule, S. D.; Diabetes Insipidus in Pregnancy, Am. J. Obst. & Gynec. **33**:878-880, 1937. (*b*) Greene, J. A., and Gibson, R. R.: Co-Existence of Diabetes Mellitus and Diabetes Insipidus: Report of Case with Pregnancy, J. Lab. & Clin. Med. **24**:455-457, 1939. (*c*) Carter, P. J.: Diabetes Insipidus in Pregnancy: Case Report, Urol. & Cutan. Rev. **44**:549-551, 1940. (*d*) Blotner, H., and Kunkel, P.: Diabetes Insipidus and Pregnancy: Report of 2 Cases, New England J. Med. **227**:287-292, 1942. (*e*) Lake, M.: Diabetes Insipidus in Pregnancy: Case with Disordered Action of Uterine Muscle (Dystocia), M. J. Australia **2**:206-209, 1947.

4. De Lee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, Ed. 8, Philadelphia, E. B. Saunders Company, 1943.

5. (*a*) McLaren, H. C., and McLeod, F. M.: A Case of Diabetes Insipidus in Pregnancy, J. Obst. & Gynaec. Brit. Emp. **49**:51-57, 1942. (*b*) Blotner and Kunkel.[3d]

6. (*a*) Maranon y Posadillo, G.: Diabetes Insipidus and Uterine Atony: Case Observed over 26 Years, Brit. M. J. **2**:769-771, 1947. (*b*) Footnote 3*a* and *c*.

7. French, H.: The Influence of Pregnancy upon Certain Medical Diseases and of Certain Medical Diseases on Pregnancy, Brit. M. J. **1**:1165-1172, 1908.

(psychogenic polydipsia). Finally, diabetes insipidus may appear after delivery. Rutledge [8] noted that diabetes insipidus appeared in a patient shortly after a premature labor.

Obstetrical Complications.—Dystocia is not by any means an invariable complication of labor in the patient with diabetes insipidus. Our cases illustrate this point, and the general experience indicated by the literature is summarized in Table 3.

Berlind [9] recorded three cases in which dystocia with difficult delivery preceded the onset of intense polydipsia, polyuria, and amenorrhea. However, it must be noted that in these patients the diagnosis of diabetes insipidus was not established by appropriate studies. According to Fisher,[10] lesions of the posterior pituitary induced in pregnant cats will result in difficult labor. Selye,[11] however, states that although the posterior lobe of the pituitary produces both antidiuretic factor and oxytocic factor only antidiuretic deficiency has been clinically manifested.

Reports also vary as to the incidence of premature labor in patients with diabetes insipidus. Our patients were delivered at term. Greene,[3b] on the other hand, stated that premature labor is frequent in patients with diabetes insipidus. Apparently this is especially true if large parenteral doses of pituitary extract are used. Carter,[3c] however, observed a full term pregnancy in spite of therapy with pituitary extract, and it is impossible, on the basis of existent knowledge, to draw any conclusions concerning this. Some are of the opinion that if pituitary extract is administered by nasal insufflation danger of premature labor is lessened.[8] Our second patient received posterior pituitary extract by injection for two months prior to delivery, which occurred at term.

TABLE 3.—*Incidence of Dystocia in Patients with Diabetes Insipidus*

	Cases, No.	Pregnancies, No.	Dystocic Labors, No.	Normal Labors, No.
Soule, S. D.[3a]	1	1	0	1
Marañon, G.[3a]	1	2	2	0
Lake, E. M.[3c]	1	2	2	0
Carter, P. J.[3c]	1	1	0	1
Greene, J. A.[3b]	1	1	0	1

A perusal of the literature suggests that no increase in fetal mortality is to be expected amongst children born of mothers having diabetes insipidus. A stillbirth was reported by Greene,[3b] cerebral hemorrhage being listed as the cause of death. The part played by the pituitary extract (given to the mother for diabetes insipidus) in the etiology of this hemorrhage is not clear, and it is the only case of its kind on record.

8. Rutledge, D. I., and Rynearson, E. H.: Diabetes Insipidus: II. Treatment by Insufflations of Powdered Posterior Pituitary Substance, Proc. Staff Meet. Mayo Clin. **14**:443-446, 1939.

9. Berlind, M.: Dystocic Labor Followed by Amenorrhea, and Diabetes Insipidus: A New Syndrome, R. Rec. **160**:731-733, 1947.

10. Fisher, C.; Magoun, H. W., and Ranson, S. W.: Dystocia in Diabetes Insipidus, Am. J. Obst. & Gynec. **36**:1-9, 1938.

11. Selye, H.: Textbook of Endocrinology, Ed. 2, Montréal Acta Endocrinologica, Université de Montréal, 1949.

The stillbirth observed in the second of our cases may have been related to the early signs of toxemia of pregnancy noted at the sixth month. The patient had not been receiving posterior pituitary extract at this time, and there was no change noted in her blood pressure, which had remained normal. It is difficult to incriminate vasopressin therapy given during the latter part of pregnancy as a cause of fetal death, because the symptoms of diabetes insipidus during this period remained despite treatment.

Anatomy and Physiology of Hypothalmic-Pituitary System.—It has been known since 1909 that the posterior lobe of the pituitary is somehow implicated in diabetes insipidus. It has also been known that a thick bundle of unmyelinated nerve fibers found in the pituitary stalk connects the posterior pituitary to the hypothalamus. It remained for Ranson and his co-workers,[12] however, to clarify the neuroanatomy of the hypothalamic-pituitary system. Using the Horsley-Clarke stereotactic instrument, these workers showed that there were nuclei in the hypothalamus which controlled the function of the cells of the posterior lobe. These nuclei, mainly the supraoptic and paraventricular, give rise to fibers which travel through the pituitary stalk to the posterior lobe. Destruction of these nuclei results in atrophy of the cells of the posterior lobe, indicating the trophic influence of the hypothalamic nuclei on the pituicytes. It is these hypothalamic nuclei together with their nerve fibers and the stalk through which the fibers travel, in addition to the cells of the posterior lobe itself, which constitute the hypothalamic-pituitary system.

It is also known that changes in the osmolarity of the intravascular fluid controls the function of this system. Verney[13] demonstrated that if hypertonic saline or dextrose solution is introduced into the vascular system the osmoreceptors of the system are stimulated by the change in osmotic gradient between the blood and the cells of the osmoreceptors. This stimulus brings about release of antidiuretic hormone from the posterior pituitary, which in turn causes increased reabsorption of water through the renal tubules and subsequent reduction of the hyperosmolarity produced by the hypertonic solution. The exact location of the osmoreceptors is not known, but many workers believe it to be supraoptic and paraventricular nuclei.

The Hare Test.—Hare[1] and Carter and Robbins[14] utilized these physiologic data as the basis of a test for diabetes insipidus. In Figures 1 and 3 it will be seen that, with the use of this technique, our patients' urinary output was not decreased appreciably by the intravenous introduction of hypertonic saline solution. It was thus indicated that the hypothalamic-pituitary system could not produce antidiuretic hormone in response to a change in osmolarity of the serum. Proof that the kidney was not at fault is provided by the drop in the urinary output in response to antidiuretic hormone. After delivery in one case, on the other hand, when polydipsia and polyuria were no longer manifested, we note that hypertonic saline resulted in a

12. Fisher, C.; Ingram, W. R., and Ranson, S. W.: The Relation of the Hypothalamico-Hypophyseal System to Diabetes Insipidus, Arch. Neurol. & Psychiat. **34**:124-163, 1935. Ranson, S. W.; Fisher, C., and Ingram, W. R.: The Hypothalamico-Hypophyseal Mechanism in Diabetes Insipidus, A. Res. Nerv. & Ment. Dis., Proc. **17**:416-432, 1938.

13. Verney, E. B.: Absorption and Excretion of Water: The Antidiuretic Hormone, Lancet **2**:739-744, 1946.

14. Carter, A. C., and Robbins, J.: The Use of Hypertonic Saline Infusions in the Differential Diagnosis of Diabetes Insipidus and Psychogenic Polydypsia, J. Clin. Endocrinol. **7**:753-766, 1947.

marked decrease in urinary output, presumably by stimulating the hypothalamic-pituitary system (Fig. 2). In the second patient the symptoms of diabetes insipidus persisted following delivery.

We wish to stress the value of this test, as well as the determination of solute concentrations in plasma and urine, in proving the presence of diabetes insipidus. These have special value during pregnancy, when various psychogenic factors may operate to produce conditions mimicking true diabetes insipidus. This is illustrated by the following case, in which the Hare test was negative, the patient having intense polydipsia with secondary polyuria during the latter half of pregnancy, on the basis of psychogenic polydipsia.

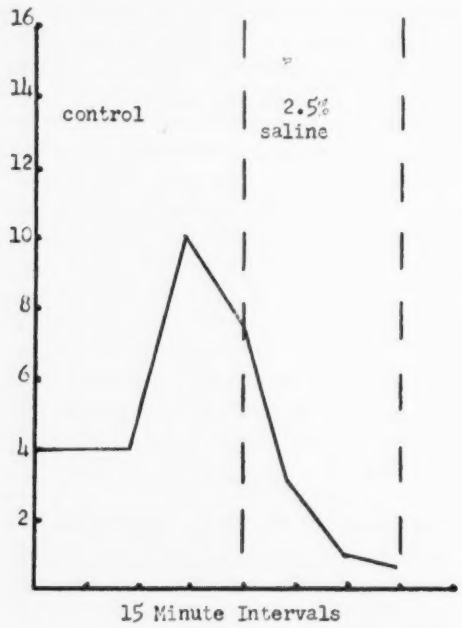

Fig. 4 (Case).—Hare test in psychogenic polydipsia.

CASE 3.—Mrs. E. I., 30 years of age, was admitted to Temple University Hospital on March 14, 1949, complaining of excessive thirst and urination of three months' duration. At this time she was approximately at term with what appeared to be a normal intrauterine pregnancy. Her last menstrual period had occurred in July 1948. She had complained also of morning vomiting and ankle swelling since November 1948. Prior to admission her urine volume had varied between 3 and 4 liters, most of which was voided during the night.

Previous medical history revealed the finding of bronchiectasis and syphilis treated four years before at another hospital. There were no other pregnancies.

Physical examination was negative except for the pregnancy; the blood pressure was 120/70. Laboratory studies revealed normal values for blood cell count and urinalysis, with specific gravities of the urine ranging from 1.001 to 1.004. The serology test for syphilis was negative. The serum chlorides were 103 mEq. per liter; serum potassium was 4.5 mEq. per liter. The blood sugar was 83 mg. and the cholesterol 370 mg. per 100 cc.; the serum albumen was 3.8 gm. and globulin was 1.8 gm. per 100 cc.

The diagnosis of diabetes insipidus was entertained initially for this patient. However, the ability to produce urine with a specific gravity as high as 1.011 during several days of her hospitalization raised some question as to the accuracy of this impression. For this reason a hypertonic saline test was performed, which gave evidence of a normal response, indicating a functioning posterior pituitary gland and adequate renal tubular activity.

During the patient's hospitalization the water intake and urine volume gradually diminished. On the basis of the above observations a diagnosis of psychogenic polydipsia was established, inasmuch as diabetes insipidus and renal disease were excluded, and the symptoms subsided during hospitalization.

The Influence of the Endocrine System on Water Metabolism.—The body control of water balance is a complicated one. It has now become apparent that, in addition to the posterior lobe of the pituitary, the anterior pituitary, the adrenal gland, the thyroid, and perhaps even the placenta, in pregnancy, may play significant roles in water metabolism.

It is interesting that in patients with Simmond's disease or Sheehan's syndrome diabetes insipidus does not develop, in spite of the fact that these conditions are associated with involution of the posterior as well as the anterior lobe of the pituitary. Von Hann, in 1918, reported 20 patients with diabetes insipidus in whom he found lesions of the posterior lobe only. In addition he recorded nine patients without anterior or posterior lobes who did not have diabetes insipidus. From these findings it appears that in order to produce diabetes insipidus the anterior lobe of the pituitary must be intact.

Richter,[15] working with rats, was able to confirm this hypothesis. He showed that complete removal of the pituitary never produced permanent diabetes insipidus, whereas removal of only the posterior lobe did have this effect in all animals. This work was later confirmed by Pencharz[16] and his group. Heinbecker,[17] working with dogs, questioned these results but did agree that if the anterior lobe is removed the polyuria is not as severe and as sustained as when it is intact.

Silvette and Britton[18] advanced the proposal that water volume is maintained as a result of the reciprocal actions of the diuretic influence of the adrenal cortex hormones and the antidiuretic effect of posterior pituitary hormone. In adrenalectomized animals Swingle and his co-workers[19] produced diabetes insipidus with cortisone, which was corrected with large doses of posterior pituitary. In the case of A. T. there was no evidence of excessive activity of the adrenal cortex during the many years of her polyuria, and the 17-ketosteroid excretion values ranged from low normal to slightly elevated levels, the latter during pregnancy.

15. Richter, C. P.: Experimental Diabetes Insipidus: Its Relation to the Anterior and Posterior Lobes of the Hypophysis, Am. J. Physiol. **110**:439-447, 1934.

16. Pencharz, R. I.; Hopper, J., Jr., and Rynearson, E. H.: Water Metabolism of the Rat Following Removal of the Anterior Lobe of the Hypophysis, Proc. Soc. Exper. Biol. & Med. **34**:14-17, 1936.

17. Heinbecker, R.; White, H. L., and Rolf, D.: The Essential Lesion in Experimental Diabetes Insipidus, Endocrinology **40**:104-113, 1947.

18. Silvette, H., and Britton, S. W.: Renal Function of the Opossum and the Mechanism of Cortico-Adrenal and Post-Pituitary Action, Am. J. Physiol. **123**:630-639, 1938.

19. Swingle, W. W.; Fedor, E. J.; Ben, M.; Maxwell, R.; Baker, C., and Barlow, G.: Induction of Diabetes Insipidus in Adrenalectomized Dogs with Cortisone, Proc. Soc. Exper. Biol. & Med. **82**:571-573, 1953.

The effect of the adrenal cortex on water metabolism has been reviewed by Gaunt.[20] Evidence of adrenal cortex participation in water balance is gained from the following observations. First, patients with Addisons's disease cannot excrete water at a proper rate, i. e., in them water intoxication easily develops. Second, agents which normally increase diuresis fail to do so in the absence of the adrenal cortex. Third, it is difficult to produce water intoxication in animals when adrenal cortex hormones are concomitantly administered. Fourth, patients with cardiac disease with water retention may have marked diuresis when large doses of lipoadrenal extract are administered. It appears then, that, in addition to the well-known salt-retaining effects of deoxycorticosterone acetate (DOCA) and the other adrenal steroids, the adrenal cortex plays a part, direct or indirect, in water diuresis. It appears that a delicately balanced mechanism of water control is inherent in the antagonist interaction of the anterior and posterior pituitary gland, the former exerting its effect on this mechanism through its trophic influence on the adrenal cortices, whose secretions in turn influence renal tubule function.

The antagonistic balance of the posterior pituitary and the anterior pituitary-adrenal axis is of even greater importance when diabetes insipidus occurs during pregnancy. From measurements of the glucocorticoid excretion during pregnancy Venning [21] concludes that the adrenal cortex is stimulated during pregnancy. She demonstrated a rise in corticoid excretion during the first trimester, followed by a decline to normal values and then by a second rise, at the fifth or sixth month, to values close to five times the normal.

The thyrotropic hormone of the anterior lobe also plays a part in controlling water balance. Heinbecker [17] reports that the administration of thyroid to a dog with diabetes insipidus will aggravate the polyuria. This is in keeping with the report of Winer,[22] who recorded a case of diabetes insipidus in which the patient was cured for six years by the development of post-thyroidectomy myxedema. It would appear, then, that the thyroid plays a significant role in the pathophysiology of diabetes insipidus. This becomes of added importance during pregnancy, since enlargement of the thyroid gland and increased thyroid activity have been demonstrated.

The placenta may play a part also in water metabolism. The report of Jailer and Knowlton [23] is especially interesting. They found an increase in corticoid excretion in a pregnant patient with Addison's disease in whom an adrenal source for this increase was fairly well eliminated. It is possible, then, that the placenta, in addition to its production of gonadotropins, estrogens, and progesterone, also produces 11- and 11, 17-oxysteroids. If this is so, another "diuretic" factor may be introduced in the water metabolism of the pregnant state. This factor, added to the other shifts in the endocrine balance referred to above, may then be responsible for the state of diabetes insipidus which was present only during pregnancy in the first patient

20. Gaunt, R.; Birnie, J. H., and Eversole, W. J.: Adrenal Cortex and Water Metabolism, Physiol. Rev. **29**:281-310, 1949.

21. Venning, E. H., and Browne, J. S. L.: Excretion of Glycogenic Corticoids and 17-Ketosteroids in Various Endocrine and Other Disorders, J. Clin. Endocrinol. **7**:79-101, 1947.

22. Winer, N. J.: Renal Runction in Diabetes Insipidus, Arch. Int. Med. **70**:61-87, 1942.

23. Jailer, J. W., and Knowlton, A. I.: Simulated Adreno-Cortical Activity During Pregnancy in an Addisonian Patient, J. Clin. Invest. **29**:1430-1436, 1950.

reported herein. It must be admitted, of course, that the increased nitrogenous waste excreted by the kidneys during pregnancy would also tend to increase the urinary output, since it is known that the polyuria of diabetes insipidus is made worse by a high protein diet.[24] However, the food intake of this patient throughout her pregnancy had been diminished. Apparently her appetite was decreased by the large amounts of water intake. Therefore, in this patient it is improbable that the solute load was increased from exogenous sources during the period when the symptoms of diabetes insipidus were manifested.

In the second patient it was apparent from the determination of solute concentration by freezing-point-lowering measurements that this factor was absent as a cause of diuresis.

SUMMARY

Two cases of diabetes insipidus occurring during pregnancy are presented. In one instance the disorder arose during the course of pregnancy and was proved by the demonstration of a positive Hare test. Following delivery the symptoms of diabetes insipidus disappeared and the Hare test became negative. The second patient, with symptoms of diabetes insipidus since infancy, was studied during her pregnancy, at the age of 16 years. She had previously manifested a severe allergic reaction to the posterior pituitary hormone administered by nasal insufflation. The determination of plasma and urine osmolarity in this patient after fluid restriction showed an abnormal response (urine : plasma osmolar ratio < 1.0) characteristic of diabetes insipidus. After delivery of a stillborn fetus the symptoms of diabetes insipidus remained. These cases are contrasted with one in which the diagnosis of diabetes insipidus was disproved during pregnancy by means of the Hare test, which was normal, thus establishing the diagnosis of psychogenic polydipsia. The possible implications of the association of diabetes insipidus and pregnancy are discussed.

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SOME STUDIES OF THE MECHANISM OF INTRACTABLE EDEMA

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THE RECENT clinical literature on the treatment of edema has emphasized the failure of certain patients to respond in the expected fashion to the usual therapeutic regimen of restriction of sodium and the use of acid diuretics such as ammonium chloride. It is of especial interest that refractoriness may develop in patients who at one time had demonstrated a good response to such diuretic programs. We have attempted to obtain further insight into the mechanisms that underlie this resistance to treatment.

In the various concepts regarding the formation of edema, diminished ability of the kidneys to excrete sodium is considered by many to be the primary factor.[1] But that such diminished urinary excretion of sodium is but a part of a general response to some stimulus acting through the adrenal cortex, rather than being primarily a result of altered renal hemodynamics, is evidenced by the accompanying low excretion of sodium in sweat,[2] saliva,[3] and feces.[4]

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2. (*a*) Eisenmenger, W. J.; Blondheim, S. H.; Bongiovanni, A. M., and Kunkel, H. G.: Electrolyte Studies on Patients with Cirrhosis of the Liver, J. Clin. Invest. **29**:1491, 1950. (*b*) Merrill.[1c]

3. White, A. G.; Gordon, H., and Leiter, L.: Studies in Edema: The Effect of Congestive Heart Failure on Saliva Electrolyte Concentrations, J. Clin. Invest. **29**:1445, 1950. Eisenmenger and others.[2a]

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The retention of water in edema appears to be brought about by increased production of the posterior pituitary antidiuretic hormone.[5] The augmented production of this substance might be activated by rising concentration of sodium in the extracellular fluid or it might be the primary change and be closely followed by increased reabsorption of sodium. In support of the first conception is the work of Verney,[6] who demonstrated increased production of the antidiuretic principle by the posterior pituitary when he injected hypertonic saline into the carotid artery. On the other hand, recent studies [7] indicate that increased production of antidiuretic hormone may develop without regard to the concentration of extracellular sodium. These two mechanisms are usually coordinated in the sense that edema fluid contains a normal concentration of sodium, but not infrequently the fluid is found to contain abnormally low concentrations of sodium.

In these studies on the mechanism of intractable edema attempts have been made to separate the two factors of sodium and water in edematous patients. During the first phase of the experiment, the effects of sodium restriction and of ammonium chloride administration were observed in a young nephritic patient with massive edema and in two healthy adults. The second phase of the experiment involved studies of the effects of water restriction on a cardiac patient with edema and ascites and on three healthy adults.

EFFECTS OF SODIUM RESTRICTION AND AMMONIUM CHLORIDE MEDICATION

About 25 years ago, several groups of workers first became interested in the effects of mineral acids and of acid-producing salts in man.[8] It was observed that during the first two or three days of administration of such substances normal kidneys responded by eliminating the acid accompanied by nearly equivalent amounts of fixed base. After this lag, ammonia, which is produced by the kidneys, supplied most of the base, with corresponding lessening of excretion of the fixed base (predominantly sodium), and it was shown that ultimately the whole contribution of base was in the form of ammonia. These observations laid the basis for the subsequent use of acid diuretics, notably ammonium chloride, in the management of edema, on

5. Robinson, F. H., Jr., and Farr, L. E.: The Relation Between Clinical Edema and the Excretion of an Antidiuretic Substance in the Urine, Ann. Int. Med. **14**:42, 1940. Ralli, E. P.; Robson, J. S.; Clarke, D., and Hoagland, C. L.: Factors Influencing Ascites in Patients with Cirrhosis of the Liver, J. Clin. Invest. **24**:316, 1945. Bercu, B. A.; Rokaw, S. N., and Massie, E.: Antidiuretic Action of the Urine of Patients in Cardiac Failure, Circulation **2**:409, 1950.

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7. (*a*) Borst, J. G. G.: The Maintenance of an Adequate Cardiac Output by the Regulation of the Urinary Excretion of Water and Sodium Chloride: An Essential Factor in the Genesis of Edema, Acta med. scandinav. (Supp. 207) **130**:1, 1948. (*b*) Leaf, A., and Mamby, A. R.: An Antidiuretic Mechanism not Regulated by Extracellular Fluid Tonicity, J. Clin. Invest. **30**:654, 1951.

8. (*a*) Gamble, J. L.; Blackfan, K. D., and Hamilton, B.: A Study of the Diuretic Action of Acid Producing Salts, J. Clin. Invest. **1**:359, 1925. (*b*) Keith, N. M., and Whelan, M.: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, ibid. **3**:149, 1926. (*c*) Linder, G. C.: The Effect of Mineral Acid on Acid-Base Regulation in Health and in Nephritis, Quart. J. Med. **20**:285, 1927. (*d*) Folling, A.: On the Mechanism of the Ammonium Chloride Acidosis, Acta med. scandinav. **71**:221, 1929.

the principle that the edema fluid is merely an excess of extracellular fluid, 90% of whose base is sodium. Gamble [8a] emphasized that the production of ammonia by nephritic kidneys under these circumstances was far less than normal and that the difference was made up by increased presence of fixed base in the urine. Accordingly, it became therapeutic practice to limit the ingestion of sodium sharply in order to avoid replenishment of sodium.

Many clinicians, including ourselves, have experienced occasional failures of this method to achieve the desired result, and opportunity has presented itself for the comprehensive study of one such patient with glomerulonephritis. He was a young edematous nephritic patient (D. M.), who had demonstrated little clinical improvement subsequent to several earlier courses of treatment with ammonium chloride and sodium restriction. Details of the case are presented in an appendix. During the entire period of accumulation of data all meals were eaten in our metabolism kitchen and medications were taken under the personal supervision of one of us. The diet contained 8.6 mEq. of sodium daily. The sodium content of this diet approximated that of the diet on which the patient had been maintained for the several weeks prior to this study. After a preliminary control period of three days, ammonium chloride was administered in a dosage of 3 gm. three times daily for two days and 3 gm. at breakfast on the third day. Because of the patient's complaints of weakness and nausea, it appeared inadvisable to administer the second and third doses on this last day. Some 390 mEq. of chloride were thus ingested in this three-day period in excess of the content of the diet. Studies were continued for a control after-period of two days, following which the patient was given mercaptomerin (Thiomerin) intramuscularly on the third and fifth days.

Two healthy adult male medical students were studied in a similar fashion. The first subject (D. K.) was maintained on a diet containing 8.6 mEq. of sodium, 138 mEq. of potassium, and 40 mEq. of chloride daily, the meals being prepared and eaten in the metabolism kitchen. After a preliminary control period of seven days, during which sodium balance was attained, ammonium chloride was administered in a dosage of 3 gm. three times daily for three days. This allowed an intake of 500 mEq. of chloride in excess of the amount contained in the diet. After a recovery period of five days, the administration of ammonium chloride was repeated in the same dosage for three days, and this was followed again by an additional five-day period of observation.

The second subject (D. N.) was placed on a similar diet (8.4 mEq. of sodium, 130 mEq. of potassium, and 40 mEq. of chloride daily), and ammonium chloride was administered in a dosage of 15 gm. daily during the first three days of the study. On the afternoon of the third day, 2 ml. of mercaptomerin was injected subcutaneously. This program was instituted with the intention of rapidly depleting the subject's stores of extracellular sodium. The following morning, after a voluminous diuresis, the subject was so weak and nauseated that a solution of sodium chloride containing 140 mEq. of sodium and of chloride was administered. Subsequently, there was emesis of the breakfast and some of the saline; all vomitus was collected and saved for analysis. An additional 100 mEq. of sodium chloride was given. The subject improved and continued on the low-sodium diet. Five days later ammonium chloride was again given in a dosage of 3 gm. three times daily for three days. A control recovery period of four days followed.

Daily 24-hour urine specimens were collected under toluene by the patient and the two subjects and were analyzed promptly for sodium, potassium, chloride, and ammonium. Creatinine was determined by the method of Bonsnes and Taussky,[9] to check the accuracy of collection. Blood was drawn (1) on the initial day, (2) prior to the administration of ammonium chloride, and (3) one hour after the last dose of ammonium chloride in each three-day period of administration and was analyzed for serum sodium, potassium, chloride, and bicarbonate. Whole blood sodium, potassium, and chloride were also determined, as well as the hematocrit level. Red cell values for sodium, potassium, and chloride were calculated by the equation of Eliel and his associates.[10] Stools were collected during the period of ammonium chloride administration and

9. Bonsnes, R. W., and Taussky, H. H.: On the Colorimetric Determination of Creatinine by the Jaffe Reaction, J. Biol. Chem. **158**:581, 1945.

10. Eliel, L. P.; Pearson, O. H., and Rawson, R. W.: Post-Operative Potassium Deficit and Metabolic Alkalosis, New England J. Med. **243**:471, 1950.

for 24 to 48 hours thereafter and were analyzed to ascertain the amount of enteric-coated ammonium chloride absorbed. Determination of sodium, potassium, and chloride in the latter was done on ashed triplicate samples of dried blended pooled stool. The internal standard flame photometer was used for all determinations of sodium and potassium.[11] Chloride analyses on the urine were done by a modification of the titration method of Volhard-Harvey,[12] and on the serum by the method of Van Slyke and Sendroy.[13] Ammonia was determined by the aeration method of Van Slyke and Cullen.[14] Serum bicarbonate was recalculated into mEq. from the CO_2-combining power, as determined by the manometric method of Van Slyke and Neill.[15]

The data on patient D. M. are shown in Table 1. Note that during the administration of ammonium chloride he not only failed to lose weight, but actually gained 2.3 kg. Clinically, the patient felt worse; he complained of nausea, lassitude, and headache, and the abdomen was noticeably more distended. That there was incomplete absorption of ammonium chloride is evident from the total of 90 mEq. of chloride recovered from the stool specimens collected during the period of NH_4Cl administration and the two days following it. However, 300 mEq. of Cl were absorbed, accompanied by a rise of the serum Cl value from 115 to 123 mEq. per liter, and the Cl content of the red cells rose from 61 to 75 mEq. per liter. Concurrently, the CO_2-combining power dropped from 14.9 to 9.9 mEq. per liter. The serum Na values remained nearly constant throughout the study, varying only from 134 to 137 mEq. per liter. The serum K rose from 5.9 to 7.6 mEq. per liter at the height of the administration of NH_4Cl. Determinations of the Na and K contents of the red cells showed definite abnormality of the electrolyte pattern before and after NH_4Cl therapy. Whereas the potassium content was low, ranging from 75 to 82 mEq. per liter of red cells (normal, 100 to 110 mEq. per liter), the sodium content was high, the average normal sodium content of red cells being 10 mEq. per liter.[16]

The renal response to the increased body content of Cl was unusual. There was only a slight augmentation of the urine volume, from 750 ml. during the foreperiod to an average of 950 ml. on the days that the patient was ingesting the acid diuretic. Likewise, the increase in the excretions of Cl, Na, and K was trivial. It is especially to be noted that there was no increase in urinary ammonia. This is seen in Table 1 by comparing the average foreperiod values with the average amounts excreted daily during the period of ammonium chloride medication. These results are in marked contrast to the response obtained when mercaptomerin was administered. With the first injection there was a copious diuresis not only of water but also of sodium and

11. Berry, J. W.; Chappell, D. G., and Barnes, R. B.: Improved Method of Flame Photometry, Indust. & Engin. Chem. (Analyt. Ed.), **18**:19, 1946.

12. Harvey, S. C.: The Quantitative Determination of Chlorides in the Urine, Arch. Int. Med., **6**:12, 1910.

13. Van Slyke, D. D.: The Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**:523, 1923.

14. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins, 1932, Vol. 2, Methods, p. 550.

15. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

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TABLE 1.—*Data on Patient D. M., Showing Responses to Ammonium Chloride Medication and to Mercaptomerin Thiomerin* *

		Blood							Urine						Stool			
		Serum				Red Cells												
Days	Body Wt., Kg.	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.	CO_2 Comb. Power, mEq./L.	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.	Na, mEq.	Cl, mEq.	K, mEq.	NH_3, mEq.	Creatinine, Gm.	Volume, Cc./24 Hr.	Na, mEq.	Cl, mEq.	K, mEq.	Medication
Foreperiod av.	42.3	134	115	5.9	14.9	40.8	61	75	5.1	12.3	25.9	18.5	0.380	750	..	..	..	.....
1	....	...	...	...	....	....	..	..	12.4	14.3	32.9	44.9	0.345	845	..	..	..	Cl, as NH_4Cl, 167 mEq.
2	....	...	...	...	....	....	..	..	16.0	34.2	47.2	6.1	0.414	1,078	..	..	..	Cl, as NH_4Cl, 167 mEq.
3	....	136	123	7.6	10.8	26.5	69	81	12.7	38.5	46.2	7.5	0.371	940	..	..	..	Cl, as NH_4Cl, 56 mEq.
4	....	...	...	...	....	....	..	..	20.5	44.2	41.4	9.2	0.390	915	..	..	..	0
5	44.6	137	123	6.5	9.9	84.1	75	82	13.5	26.5	29.4	8.6	0.380	418	..	..	..	0
Totals	+2.3	...	...	...	....	....	..	..	75	116	197	75	.....	.....	20	90	92	390
Daily av.	....	...	...	...	....	....	..	..	15	32	39	15	.....	.....	..	..	..	.....
6	....	...	...	...	....	....	..	..	191	220	35	15.6	0.460	2,035	..	..	..	Mercaptomerin, 1 cc.
7	....	...	...	...	....	....	..	..	116	144	41	11.7	0.418	1,450	..	..	..	.....
8	42.0	136	113	5.8	9.9	71.3	66	91	87	122	46	9.8	0.418	1,298	..	..	..	Mercaptomerin, 1 cc.
Totals	−2.6	...	...	...	....	....	..	..	394	486	122	37.1	.....	.....	..	..	..	.....
Daily av.	....	...	...	...	....	....	..	..	131	162	41	12.4	.....	.....	..	..	..	.....

* Daily intake of Na was 5 mEq. and of Cl was 7 mEq.

TABLE 2.—*Data on Normal Subject R. K., Showing Responses to Two Consecutive Periods of Ammonium Chloride Medication While on a Sharply Restricted Sodium Intake*

			Blood							Urine						Stool			
			Serum				Red Cells												
Periods	Day	Body Wt., Kg.	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.	CO_2-Comb. Power, mEq./L.	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.	Na, mEq.	Cl, mEq.	K, mEq.	NH_3, mEq.	Creatinine, Gm.	Volume, Cc./24 Hr.	Na, mEq.	Cl, mEq.	K, mEq.	Remarks
Foreperiod	0	84.3	142	104	4.7	30	18.9	56.5	99.8	151	175	114	44	2.25	2,590	...	....	..	Usual diet, uncontrolled
I. 7 days Na restriction	7	82.8	143	101	5.0	28	20.4	59.4	102.1	2	19	119	31	2.17	1,180	...	....	..	200 mg. Na diet throughout experiment
II. NH_4Cl first 3 days	8	82.9	...	...	...	..	....	....	....	9	66	141	46	2.16	1,740				Cl, as NH_4Cl, 167 mEq.
	9	82.6	...	...	...	..	....	....	....	44	178	162	71	2.39	1,615	0.4	0.18	26	Cl, as NH_4Cl, 167 mEq.
	10	82.0	137	103	5.6	22	18.1	62.9	95.4	51	198	154	88	2.06	2,100				Cl, as NH_4Cl, 167 mEq.
	11	81.9	...	...	...	..	....	....	....	24	143	130	94	2.35	1,210				.....
	12	82.1	...	...	...	..	....	....	....	5	72	80	83	2.36	1,270	...	....	..	.....
	13	82.3	...	...	...	..	....	....	....	4	57	83	71	2.28	1,570	...	....	..	.....
	14	82.7	...	...	...	..	....	....	....	1	34	88	54	2.16	940	...	....	..	.....
	15	82.7	142	99	5.1	29	14.2	54.5	98.6	0.9	32	118	40	2.06	1,390	...	....	..	.....
Urinary increases	..	....	...	...	...	..	....	....	....	123	628	4	299	....	.....	...	....	..	.....
III. NH_4Cl first 3 days	16	82.7	...	...	...	..	....	....	....	4	60	132	43	2.18	1,880	...	....	..	Cl, as NH_4Cl, 167 mEq.
	17	81.9	...	...	...	..	....	....	....	22	172	171	70	2.31	1,835	...	....	..	Cl, as NH_4Cl, 167 mEq.
	18	81.6	138	104	5.7	24	12.3	58.9	97.2	31	187	167	85	2.34	2,085	...	....	..	Cl, as NH_4Cl, 167 mEq.
	19	81.6	...	...	...	..	....	....	....	16	133	126	85	2.31	1,620	...	....	..	.....
	20	81.7	...	...	...	..	....	....	....	3	73	90	82	2.37	1,500	...	....	..	.....
	21	82.0	...	...	...	..	....	....	....	1	42	72	63	2.09	1,375	...	....	..	.....
	22	82.3	...	...	...	..	....	....	....	0.8	35	86	48	2.01	1,220	...	....	..	.....
	23	82.2	...	...	...	..	....	....	....	0.5	28	115	31	2.20	1,135	...	....	..	.....
Urinary increases	..	....	...	...	...	..	....	....	....	62	578	7	259	....	.....	...	....	..	.....

chloride. The average daily sodium excretion of 15 mEq. during the ammonium chloride regimen increased to 191 mEq., and the chloride value from 32 mEq. to 220 mEq. The response to a second dose of mercaptomerin two days later was less dramatic as far as the electrolyte excretion was concerned; nevertheless, after the two injections, the cumulative weight loss amounted to 2.6 kg.

In Table 2 are presented the data on the normal subject R. K. There was a remarkably good absorption of NH_4Cl, as evidenced by a total four-day excretion in the stool of only 0.18 mEq. of chloride during the first period. The doubling of the stool values for Cl, Na, and K during the second period may be attributed to one mushy stool. There was a weight loss of 0.9 kg. immediately following the first trial of NH_4Cl and of 1.1 kg. accompanying the second. In marked contrast to the patient, the control subject excreted quantitatively all of the Cl ingested as NH_4Cl in four days (during the three days of NH_4Cl administration and the day after). This was accompanied by a corresponding increase in Na and K excretion amounting to a total of 119 mEq. for the former and 110 mEq. for the latter. Ammonia production lagged for a day or two, then was increased considerably during the last day of NH_4Cl administration and for several days thereafter. The calculated total increase in ammonia production during the four days under consideration was 176 mEq. As shown in Table 2, the calculated urinary increases for the eight-day period (three days NH_4Cl administration and five days of recovery) are as follows: sodium, 123 mEq.; chloride, 628 mEq.; potassium, 4 mEq., and ammonia, 299 mEq.

During the second period of NH_4Cl medication there was again an increase in the urinary excretions of Cl, Na, and K and in the production of ammonia, but with this difference: the increase in sodium excretion during this second eight-day period amounted to only 62 mEq., or 11%, of the increase in urinary Cl, as compared with 123 mEq., or 19%, of the increase in urinary Cl during the first period.

The NH_4Cl administered to the normal subject induced the usual changes in the blood electrolyte values. The red cell Cl in particular increased only from 59.4 to 62.9 mEq. per liter during the first period and from 54.5 to 58.9 mEq. per liter during the second. There was a slight but consistent drop in the concentration of serum sodium in both instances, amounting to 6 mEq. per liter during the first period and to 4 mEq. per liter with the second run.

The results of the electrolyte studies on the second normal subject, D. N., are shown in Table 3. The administration of 15 gm. of ammonium chloride daily for three days as well as the injection of 2 ml. of mercaptomerin caused such a copious diuresis of sodium that by the end of the fourth experimental day a negative sodium balance of 428 mEq. had resulted. If we allow a daily skin loss of 10 mEq. of sodium, the total negative balance would be 468 mEq. If the concentration of sodium in the extracellular fluid had been 140 mEq. per liter and the water and sodium were lost in these proportions one would expect a total depletion of water of 3.3 liters. It is interesting that the actual weight loss by the end of this period was 3.7 kg. It is to be noted that during the first period of ammonium chloride medication, when there had been no previous sodium restriction, sodium contributed 50% of the base required for chloride excretion. When ammonium chloride was administered a second time, four days later, the increase in urinary sodium excretion was so trivial that it accounted for only 2% of the increase in chloride excretion.

TABLE 3.—*Data on Normal Subject D. N., Showing Response to Standard Doses of Ammonium Chloride Following Rapid Depletion of Body Sodium by Administration of Large Doses of Ammonium Chloride and of Mercaptomerin (Thiomerin) While on a Sharply Restricted Sodium Intake*

			Blood							Urine						Stool			
			Serum				Red Cells												
Periods	Days	Body Wt., Kg.	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.	CO_2 Comb. Power, mEq./L.	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.	Na, mEq.	Cl, mEq.	K, mEq.	NH_3, mEq.	Creatinine, Gm.	Volume, Cc./24 Hr.	Na, mEq.	Cl, mEq.	K, mEq.	Remarks
Foreperiod	0	74.5	142	104	4.4	27	11.7	54.1	97.8	...	...	...	..	....	.....	..	..	..	Usual diet, uncontrolled
I. NH_4Cl first 3 days and	1	73.1	...	...	..	..	....	....	....	186	291	138	59	2.05	2,000				200 mg. Na diet throughout; Cl, as NH_4Cl, 280.5 mEq. daily during first 3 days
2 ml. mercaptomerin on	2	72.7	...	...	...	..	....	....	....	115	294	167	98	1.95	1,915	7	47	32	
3d day	3	70.2	136	107	5.1	20	17.1	54.6	93.5	348	588	203	124	1.71	4,270				
	4	70.8	139	...	...	..	....	....	....	7	84	64	130	1.77	1,320				
	5	71.4	...	...	...	..	....	....	....	1	66	47	130	1.85	1,655	..	..	..	.....
	6	71.7	...	...	...	..	....	....	....	0.3	46	43	106	2.00	1,410	..	..	..	.....
	7	72.2	138	98	6.0	30	12.7	48.9	92.9	0.5	45	55	92	1.98	1,925	..	..	..	.....
Urinary increases	..	....	...	...	...	..	....	....	....	644*	1,281*	−116*	522*	....	.....	..	..	..	.....
II. NH_4Cl first 3 days	8	71.9	...	...	...	..	....	....	....	3	80	96	82	1.94	1,140				Cl, as NH_4Cl, 167 mEq. during first 3 days
	9	71.6	...	...	...	..	....	....	....	6	155	156	97	1.86	1,740	3	3	37	
	10	71.4	141	105	5.8	38	10.4	54.6	90.8	10	168	193	94	1.90	1,775				
	11	71.1	...	...	...	..	....	....	....	3	106	113	94	2.06	1,795				
	12	71.5	...	...	...	..	....	....	....	0.8	65	70	88	1.85	1,210	..	..	..	.....
	13	72.0	...	...	...	..	....	....	....	0.4	44	77	64	1.92	1,015	..	..	..	.....
	14	72.1	...	...	...	..	....	....	....	0.5	37	91	46	1.98	1,435	..	..	..	.....
Urinary increases	..	....	...	...	...	..	....	....	....	10*	522*	−37*	348*	....	.....	..	..	..	.....

* Since subject D. N. was given NH_4Cl on the first day of dietary sodium restriction, these urinary increases were calculated by using the urinary values obtained from subject R. K. on the day preceding NH_4Cl medication. Subject R. K. was on a diet similar to that of D. N.

COMMENT

Within recent years it has been firmly established that a sharp restriction of the intake of sodium stimulates the adrenal cortex mechanism which governs the reabsorption of this electrolyte from the renal tubular fluid.[16b] This results in a diminishing urinary content of sodium to such an extent that even when the dietary intake of it is radically curtailed, urinary sodium in the course of a week is reduced sufficiently to reestablish sodium balance. In the case of the normal subject, R. K., the urinary sodium on the seventh day of an intake of 8.6 mEq. (200 mg.) had fallen to 2.3 mEq. (53 mg.).

Since the excretion of administered chloride requires a nearly equivalent addition of total base to the urine, it is interesting that only 19% of the total increase in urinary chloride during the first course of ammonium chloride administration was met by sodium in the case of the normal control subject, R. K. This loss of sodium resulted in a further depletion of body sodium and apparently acted as an increased stimulus to the mechanism that governs its reabsorption, since five days after the last dose of ammonium chloride the urinary sodium had declined to 0.9 mEq.

This was the condition when ammonium chloride was administered the second time. Presumably, the greater depletion of body sodium accounts for the lessening of the sodium contribution to total base excretion. It is to be noted that during the second period only 62 mEq. of sodium appeared in the urine, as compared to 123 mEq. during the first period of ammonium chloride administration.

The effect of preceding depletion of body sodium on the response to ammonium chloride medication is even more clear cut in the case of the normal control subject D. N. On the fourth day after cessation of ammonium chloride and mercaptomerin medication the urinary sodium fell to 0.5 mEq. When ammonium chloride was administered for a second time, on the following three days, the urinary sodium excretion increased by only 10 mEq., as compared to an increase of 644 mEq. during the first period.

These data obtained from the control subjects suggest that the failure of some patients to excrete much sodium during ammonium chloride medication is due to the increased activity of the adrenal cortex mechanism brought about by the preceding long restriction of sodium intake. This view is supported by the recent work of Luetscher and Deming,[17] who depressed the adrenal cortex mechanism in edematous patients by giving them large doses of cortisone. Immediately after withdrawal of the hormone, many of their patients experienced a large diuresis.

During the five-day period in which patient D. M. received ammonium chloride for the first 3 days only 100 mEq. of the 300 mEq. of chloride absorbed were excreted in the urine. There was no increased excretion of ammonia during this period. Since it is well established that the ability of the kidneys to produce ammonia becomes less and less as the renal disease advances and since this patient was in the terminal phase of glomerulonephritis, the low urinary ammonia can be properly attributed to the severity of the renal lesion. The increase in urinary sodium during this five-day period amounted to a total of only 50 mEq. As already pointed out, the failure of the patient to excrete significantly increased

17. Luetscher, J. A., Jr., and Deming, Q. B.: Treatment of Nephrosis with Cortisone, J. Clin. Invest. **29**:1576, 1950.

amounts of urinary sodium may be attributed to the preceding prolonged sharp restriction of dietary sodium. Accordingly, to eliminate the ingested chloride by renal excretion, increased amounts of fixed base other than sodium would have to appear in the urine. We did not measure calcium or magnesium excretion. The urinary potassium increased by 65 mEq. during the five-day period under consideration.

The excretion of small amounts of sodium when the need for base to eliminate the chloride was great indicates that its reabsorption by the tubules was very effective. This could come about only as a result of tubular osmotic work,[18] as is indeed shown in Table 4. When this function was interfered with by the administration of a mercurial diuretic which acts by transient injury to the tubule cells, the tubular osmotic work was strikingly lessened. As a result, less sodium was reabsorbed and more of it came out in the urine. These data support the view that the effective tubular reabsorption of sodium accounted for the trivial increase in sodium excretion during ammonium chloride administration.

TABLE 4.—*Data Comparing Renal Tubular Osmotic Work Done on Sodium During Ammonium Chloride and During Mercaptomerin (Thiomerin) Medication in Patient D. M.*

Day	Medication	Renal Tubular Osmotic Work* on Sodium, Gm. Cal.
1.	NH_4Cl, 9.0 Gm.	45.6
2.	NH_4Cl, 9.0 Gm.	59.0
3.	NH_4Cl, 3.0 Gm.	63.5
Av.		56.0
6.	Mercaptomerin, 1 cc.	10.2
7.		12.7
8.	Mercaptomerin, 1 cc.	17.4
Av.		13.4

* Calculated by von Rhorer's equation,[18] Work $= NRT \times \left[(2.3 \log u/B) - \frac{u - B}{u}\right]$, where N = gram molecular weight of an excreted substance; R = the gas constant (1.987 cal. per degree); T = absolute body temperature (37 C. + 273 C. = 310 C.); u = concentration of the substance in the urine; B = concentration of the substance in the blood, and 2.3 = factor to convert common to natural logs.

EFFECTS OF WATER RESTRICTION

Since the organism will continue to lose water by evaporation from the lungs and skin, even though the supply of water is drastically reduced, a loss of body water will take place. This might be accompanied by loss of sodium through urinary excretion in amounts proportional to its concentration in the extracellular fluid. Should this take place, the major change would consist of a reduction in the volume of the extracellular fluid, including the blood volume.

However, the depletion of body water may not be accompanied by large losses of sodium. In that case, the increasing concentration of the extracellular fluid abstracts water from the intracellular compartment, thus maintaining osmotic equilibrium throughout the system.

In the presence of edema, one might anticipate that the patient whose intake of sodium and water is drastically reduced would excrete the sodium previously

18. von Rhorer, L.: Über die osmotische Arbeit der Nieren, Arch. ges. Physiol. **109**:375, 1905.

allocated to the water which he is losing by evaporation, since he already has an excess of these entities (sodium and water) in his body. If this outcome occurred, a method for removal of edema in patients in whom other methods had failed would be at hand. We have put these ideas to the test on a patient with heart disease with edema and ascites.

An adult patient with cardiac disease (H. K.), who had suffered repeated episodes of decompensation (see appendix), had failed to attain an effective response to sodium restriction plus the administration of ammonium chloride. A weight loss of 6.4 kg. prior to the onset of the study was largely attributable to repeated paracenteses. Ascites and edema were still present when this patient was placed on a dry diet with a total water content of 75 gm. daily. It consisted mainly of peanuts, bread, butter, sugar, and hard candy. This diet was calculated to contain 0.5 mEq. of sodium, 44 gm. of protein, and 2,200 calories. After three days on this diet, during which time no thirst was noted, the patient was returned to a low sodium diet containing approximately 9 mEq. of sodium with water ad libitum. Finally, he was returned to the experimental diet containing only 0.5 mEq. of sodium, which was maintained for five days. But during this last period he received 2,000 ml. of distilled water daily in addition to the water content of the diet. On each of the last two days of this five-day period, 2 ml. of mercaptomerin was administered by subcutaneous injection.

Three normal healthy adults were studied in a similar fashion. Subjects D. H. and J. G. were maintained on a diet containing approximately 9 mEq. of sodium for seven days and then were placed on the dry diet containing 0.5 mEq. of sodium and with a total water content of 75 gm. daily. Water and electrolyte balances were calculated for the subsequent three-day period.

In a further phase of this experiment, subjects J. G. and H. H. were fed a constant diet containing a moderately large quantity of sodium (134 mEq. daily in the case of J. G.; 148 mEq. daily in the case of H. H.). After four days on this diet without water restriction, drinking water was withdrawn for a two-day period while the same diet was continued. Total daily water content of the diet was estimated to be 510 gm. for J. G. and 720 gm. for H. H. The experiment was concluded with a two-day recovery period, when water was ingested ad libitum, the diet otherwise continuing unchanged.

Collection of 24-hour urine samples was carried out and analyses performed as described above. Blood specimens were drawn (1) on the initial day, (2) prior to the start of water restriction, and (3) just prior to the return to an unlimited water intake. In addition to the studies described previously, serum proteins were determined by a modification of the method of Weichselbaum.[19]

Table 5 gives the experimental data on the cardiac patient, H. K., and on the healthy adults, J. G., D. H., and H. H., all of whom were subjected to water restriction under varying conditions of sodium intake.

During the three-day period that patient H. K. was on the dry diet (total water content, 75 gm.; Na, 0.5 mEq.), he lost 3.46 kg. of body weight. This diet provided adequate calories for maintenance of weight; consequently the weight loss can be attributed to loss of body water. During this three-day period, the increase in urinary sodium excretion was strikingly small, amounting to only 13 mEq. over the foreperiod value. The serum sodium concentration increased from 137 mEq. per liter before the patient went on the dry diet to 148.8 mEq. per liter at the end of the period. Similarly, the serum chloride concentration rose from 102.7 to 110.5 mEq. per liter. Note that the red cell values for sodium, chloride, and potassium rose accordingly.

19. Weichselbaum, T. E.: An Accurate and Rapid Method for the Determination of Proteins in Small Amounts of Blood and Plasma, Am. J. Clin. Path. **16:** (Tech. Sec., 10:40-49), 1946.

TABLE 5.—*Data Showing Responses of Patient H. K. and of Normal Subjects J. G., D. H., and H. H. to Water Restriction*

Subject	Experimental Day	Body Wt., Kg.	Blood: Hematocrit Level, %	Blood: Serum: Proteins, Gm./100 Cc.	Blood: Serum: Na, mEq./L.	Blood: Serum: Cl, mEq./L.	Blood: Serum: K, mEq./L.	Blood: Serum: Creatinine, Mg./100 Cc.	Blood: Red Cells: Na, mEq./L.	Blood: Red Cells: Cl, mEq./L.	Blood: Red Cells: K, mEq./L.	Urine: Volume, Ml./24 Hr.	Urine: Specific Gravity	Urine: Na, mEq.	Urine: Cl, mEq.	Urine: K, mEq.	Urine: Total N, Gm.	Urine: Creatinine, Gm.	Urine: Glomerular Filtrate Vol. L./24 Hr./1.73 Sq. M.	Remarks
H. K.	Foreperiod																			
(S. A.	(Daily av.)	62.1	43.1	....	137.0	102.7	6.3	0.96	10.3	56.3	103.5	1,725	.....	0.8	10.5	34.9	7.4	0.936	97.5	
1.73),	1	60.9	....	....	.....	.....	....	....	....	....	.....	445	1.021	1.6	20.9	36.8	6.1	0.830	....	Start of dry diet; no drinking H_2O
cardiac	2	59.8	....	....	.....	.....	....	....	....	....	.....	325	1.029	3.1	23.0	29.7	5.1	0.696	....	(H_2O content 75 gm., Na 10 mg.,
disease	3	58.7	42.9	....	148.8	110.5	4.8	0.90	15.9	58.9	108.3	385	1.027	10.0	36.3	38.1	6.2	0.824	91.6	calculated)
	6	62.8	45.2	....	138.0	100.9	5.6	0.96	9.7	55.2	102.5	.....	.....	....	....	....	....	.....	....	Ward diet, 8.6 mEq. Na
	7	62.5	...	...	.....	.....	....	....	....	....	.....	1,260	1.011	0.3	3.0	30.4	7.6	0.800	....	Dry diet plus 2,000 cc. H_2O
	8	62.5	...	...	....	.....	....	....	....	....	.....	1,020	1.012	0.3	4.1	20.9	6.8	0.806	....	
	9	62.2	....	....	.....	.....	....	....	....	....	.....	1,288	1.010	0.3	3.8	21.7	7.9	0.886	....	
	10	60.7	....	....	.....	.....	....	....	....	....	.....	2,575	1.011	116.0	251.2	114.5	7.3	0.824	....	Mercaptomerin 2 cc.; dry diet plus 2,000 cc. H_2O
	11	60.2	....	....	.....	.....	....	....	....	....	.....	1,390	1.012	48.8	114.7	59.5	6.8	0.855	....	Mercaptomerin 2 cc.
	13	62.0	43.3	....	131.8	90.0	5.0	1.25	7.6	46.1	106.6	1,820	1.008	0.4	1.9	45.3	7.2	0.928	74.2	Second day on 150 mg. Na, unrestricted H_2O
J. G.	Foreperiod	49.9	45.0	7.13	145.8	104.7	4.6	1.01	13.4	58.0	98.9	980	1.024	87.2	100.7	95.1	....	1.196	141.3	Usual uncontrolled diet
(S. A.	5	49.0	....	....	.....	.....	....	....	....	....	.....	.....	.....	5.1	17.1	70.3	....	1.079	....	Fifth day on 200 mg. Na diet
1.45),	6	49.2	44.5	7.16	142.8	100.8	4.7	0.95	11.0	54.4	94.1	925	.....	5.9	12.9	59.7	10.0	1.170	147.0	
normal	7	48.3	....	....	.....	.....	....	....	....	....	.....	405	1.038	8.0	5.8	50.3	8.6	1.032	....	Start of dry diet (H_2O content 75 gm.,
	8	47.4	....	....	.....	.....	....	....	....	....	.....	330	1.048	9.6	8.7	45.0	7.4	1.032	....	Na content 10 mg., calculated)
	9	46.6	44.0	7.72	141.5	107.5	4.5	1.05	25.5	55.2	102.5	323	1.042	30.1	19.1	34.0	7.3	1.009	114.6	
D. H.	Foreperiod	55.2	49.0	6.86	147.3	106.2	4.3	1.05	20.2	58.9	101.2	1,875	1.014	157.9	169.7	83.1	....	1.472	151.6	Usual uncontrolled diet
(S. A.	5	....	....	....	.....	.....	....	....	....	....	.....	.....	.....	3.2	10.9	81.2	....	1.352	....	Fifth day on 200 mg. Na diet
1.60),	6	54.0	49.0	6.97	145.8	101.7	4.6	....	14.7	52.2	.....	1,370	.....	3.2	11.0	69.9	12.0	1.439	144.0	
normal	7	53.0	....	....	.....	.....	....	....	....	....	.....	463	1.030	0.7	4.7	57.1	8.8	1.343	....	Start of dry diet (H_2O content 75 gm.,
	8	52.3	....	....	.....	.....	....	....	....	....	.....	425	1.033	6.8	8.2	40.5	9.7	1.386	....	Na 10 mg., calculated)
	9	51.6	51.0	7.39	144.8	104.5	5.1	1.54	20.6	55.7	95.5	305	1.044	6.7	10.8	43.5	7.5	1.287	90.4	
J. G.,	Foreperiod	52.2	43.4	6.72	142.3	103.0	4.6	0.85	19.5	56.5	102.3	.....	.....	....	....	....	....	.....	168.7	Usual uncontrolled diet
normal	1-4	52.2	....	....	.....	.....	....	....	....	....	.....	.....	.....	....	....	....	....	.....	....	134 mEq. Na diet throughout
	(Daily av.)	51.6	43.2	6.56	139.0	105.7	4.3	0.82	18.1	53.0	102.9	970	1.016	160.7	140.4	56.6	9.5	1.207	175.6	
	5	50.7	....	....	.....	.....	....	....	....	....	.....	780	1.024	181.6	175.0	74.6	8.6	1.221	....	No drinking H_2O
	6	50.0	42.6	7.05	143.0	108.8	4.3	0.94	14.8	56.9	101.5	640	1.028	153.6	156.2	82.8	9.1	1.192	151.3	No drinking H_2O
	7	51.6	....	....	.....	.....	....	....	....	....	.....	540	1.025	60.1	75.8	54.9	....	1.204	....	Water ad libitum
	8	51.6	39.4	6.27	137.8	104.5	4.5	0.90	12.9	58.0	98.2	745	1.023	116.8	105.6	68.1	....	1.257	166.7	Water ad libitum
H. H.	Foreperiod	87.2	49.1	7.15	144.5	105.2	4.9	1.10	22.4	47.7	91.3	.....	.....	....	....	....	....	.....	167.5	Usual uncontrolled diet
(S. A.	1-4	87.2	....	....	.....	.....	....	....	....	....	.....	.....	.....	....	....	....	....	.....	....	
1.83,	(Daily av.)	86.7	49.5	7.22	137.5	102.4	4.7	1.08	18.2	53.5	94.6	1,410	1.014	152.7	151.7	68.2	12.2	1.977	173.0	148 mEq. Na diet throughout
ideal),	5	85.5	....	....	.....	.....	....	....	....	....	.....	670	1.028	124.5	147.5	78.4	10.1	2.157	....	No drinking H_2O
normal	6	84.7	49.1	7.50	148.0	109.0	4.5	1.28	16.5	52.4	99.0	675	1.031	122.9	155.7	114.8	11.3	2.160	159.5	No drinking H_2O
	7	87.0	....	....	.....	.....	....	....	....	....	.....	620	1.028	65.7	58.5	53.4	....	1.941	....	Water ad libitum
	8	87.5	46.5	6.80	141.3	104.5	4.8	1.12	10.3	51.9	96.7	1,210	1.011	147.2	72.7	29.1	....	2.000	168.8	Water ad libitum

Normal subjects J. G. and D. H. who were placed on the same dry diet for three days, after previous restriction of sodium intake to 8.6 mEq. daily for seven days, gave a response that was similar to that of patient H. K. Over a short period of three days, both of them lost body weight, to the extent of 2.6 kg. in the case of J. G. and 2.4 kg. in the case of D. H. Thirst was so marked that they were unable to eat all of the diet during the last two days. During this three-day period the increase in urinary sodium over the foreperiod value was only 30 mEq. in the case of J. G. and 4.6 mEq. in the case of D. H. There was no significant change in the serum sodium concentration in either of them.

In the second phase of the experiment, subjects J. G. and H. H. were subjected to water restriction for two days while subsisting on diets containing the usual amounts of sodium. While both of them lost weight rapidly on this regimen (1.6 kg. for J. G. and 3.0 kg. for H. H.), the expected diuresis of sodium again failed to occur. It is interesting that both of them showed a significant drop in the urinary excretion of sodium, chloride, and potassium on the first day that water was allowed ad libitum following water restriction. The serum sodium concentration in J. G. rose from 139 mEq. per liter before water restriction to 143 mEq. per liter at the height of water restriction. A similar rise from 137.5 to 148 mEq. per liter took place in subject H. H.

While subsisting on the dry diet the normal subjects suffered from intense thirst, whereas the edematous patient with cardiac disease did not complain of it. The following calculations show that in the normal control subjects a transfer of water from the intracellular to the extracellular compartment occurred, whereas in the patient there was no such shift of water:

Normal subject J. G. lost 2.6 kg. of water through evaporation during the three-day period. Since the serum sodium concentration was 142 mEq. per liter, 369 mEq. of sodium were originally distributed through the evaporated water. From this quantity are subtracted 30 mEq., which was the increase in urinary sodium excretion during the three-day period, and 29 mEq., which is the amount of sodium that entered the red cells (red cell sodium concentration increased from 11 to 25.5 mEq. per liter and the total red cell volume was estimated to be two liters). After the subtractions are made, 310 mEq. of sodium still remain to be accounted for. Since there was no significant change in the concentration of sodium in the extracellular compartment during this period, 2.2 liters of water (310 divided by 142) must have been transferred from the intracellular to the extracellular space. This is about 10% of the estimated 24.5 liters of intracellular fluid in subject J. G.

Calculations from the data on normal subject D. H. show that a similar transfer of 2.3 liters of water occurred.

In patient H. K. 442 mEq. of sodium remain to be accounted for after subtracting 13 mEq., which was the increase in urinary sodium excretion, and 11 mEq., which went into the red cells. The concentration of serum sodium increased by 11.8 mEq. per liter. Four hundred and forty-two divided by 11.8 gives 37 liters, in which 442 mEq. of sodium had to be dispersed in order to account for the increase in its extracellular concentration. This patient could easily have had 37 liters of extracellular fluid, since he was markedly edematous and had a great accumulation of abdominal fluid. We made no attempts to measure extracellular

space, but, since thirst is believed by several investigators [20] to be a clinical manifestation of intracellular water depletion, the absence of thirst in the patient would support our assumption that no significant shift of water from the intracellular to the extracellular space took place.

Comment

It is again pointed out that the normal subjects did not excrete sodium that was released by loss of body water, and this may be interpreted as evidence of the existence of a mechanism designed to maintain a certain volume of extracellular fluid, which in these cases was successful, since water was transferred from the cells in amounts sufficient to replenish that lost from the extracellular space through evaporation. In the case of the patient who had an abnormally large extracellular volume, water was not transferred from the cells to the extracellular space, as evidenced by the increase in the concentration of serum sodium.

In the second phase of this experiment, when the usual amounts of sodium were ingested but no drinking water was allowed, there again was no increase in urinary sodium, despite a loss of body water of 2 kg. for normal subject H. H. and 1.6 kg. for normal subject J. G. These results were surprising because it was thought that the lack of increase in excretion of urinary sodium in the first phase of the experiment was a response to the previous sharp restriction of dietary sodium.

As before, calculations show that there was a transfer of water from the cells to the extracellular space. Otherwise the serum sodium concentration in subject H. H. would have risen by 18 mEq. per liter instead of 10 mEq., and by 19 mEq. instead of only 4 mEq. per liter in the case of subject J. G. This again affords evidence of the existence of a mechanism designed to maintain extracellular fluid volume.

Since edema is the result of excessive accumulation of salt and water, one must assume that this change comes about primarily either by failure to excrete these substances or as a result of increased reabsorption of them by the renal tubules. Our studies indicate that both the patients with nephritis and those with heart disease possessed a very efficient mechanism for the reabsorption of sodium, since when the organism already contained an abnormally large amount of sodium it succeeded in maintaining sodium balance even when the intake of sodium was minimal. These studies have, in fact, shown that the sodium filtered through the glomeruli was recovered by the renal tubules by osmotic work. The dependence of the retention of body sodium on tubular osmotic work is demonstrated by the response to the mercurial diuretic, mercaptomerin. This substance injures the cells temporarily, and during the period of its activity the ability to do osmotic work was so greatly reduced that large amounts of sodium, accompanied by proportional amounts of water, appeared in the urine.

This osmotic work of the renal tubule cells results in a surprisingly large reabsorption of sodium in both the control subjects and the patients even when unavoidable loss of body water takes place. This is contrary to what was anticipated in regard to the patients, since it was expected that removal of body water

20. Dill, D. B.: Life, Heat, and Altitude: Physiological Effects of Hot Climates and Great Heights, Cambridge, Mass., Harvard University Press, 1938. Marriott, H. L.: Water and Salt Depletion, Springfield, Ill., Charles C Thomas, Publisher, 1950.

from an edematous person would be accompanied by a proportional urinary excretion of sodium. Since normal subjects demonstrated the same resistance to the loss of sodium when they were forced to lose body water, one may regard this phenomenon as a mechanism for maintaining an effective extracellular volume. Since a similar response was shown by the edematous patient, it is suggested that the increased extracellular volume serves a useful purpose. In fact, the literature contains studies [7a] which in our view show that edema is a beneficial accumulation of extracellular fluid, since this occurrence tends to prevent circulatory failure.

SUMMARY

Data on two normal subjects emphasize again the ability of the organism to conserve sodium by tubular reabsorption of nearly all of it contained in the glomerular filtrate when only minimal amounts of sodium are ingested.

After this condition had been instituted in one of the normal subjects by sharp restriction of dietary sodium, chloride was administered, whose urinary excretion requires a nearly equivalent appearance of total base in the urine, and less than one-fifth of the base requirement was supplied as sodium. During a second period of ammonium chloride administration, while the sodium intake was still restricted, the urinary sodium was even less. In another healthy subject, following a regimen that caused a marked and rapid depletion of body sodium, the contribution of sodium accompanying the increased urinary excretion of chloride, administered as NH_4Cl, fell to only 2%.

The edematous nephritic patient reacted to the administered chloride by excreting only 20% of it. This might be explained by the inability of the kidneys to increase production of ammonia and by the small contribution of sodium due to its very efficient reabsorption by the tubules. When tubular reabsorption of sodium was depressed by administration of a mercurial diuretic, the plentiful appearance of sodium in the urine without increase in ammonia was accompanied by a large excretion of chloride.

Studies conducted on an edematous patient with heart disease and on two normal subjects showed that under conditions of water restriction, when body water is forcibly lost through evaporation, the anticipated proportionate loss of sodium through the urine did not occur. On the contrary, calculations show that a large transfer of water from the cells into the extracellular space took place in the normal persons. In the edematous patient with heart disease no such transfer was demonstrated.

These studies indicate that both the patients with nephritis and those with cardiac disease possessed a very efficient mechanism for the renal tubular reabsorption of sodium. Since in both of the patients the volume of the extracellular fluid was excessive, one is led to conclude that the stimulus which resulted in reabsorption of sodium and water had become greatly increased. The mechanism itself in such patients may be normal and the change be merely quantitative.

More study will be required to decide under what circumstances edema is the expression of a stimulus that causes coordinated increased production of both the antidiuretic and the adrenal cortex hormones, or whether the stimulus acts primarily on one of them, followed by a response on the part of the other one.

APPENDIX

Report of Cases

D. M., a 14-year-old boy, was first admitted to University Hospital on Oct. 6, 1950. He felt perfectly well until March, 1950, when an ear infection developed, which was treated by penicillin injections. Following this, the patient was well until April. At that time he complained of right lower quadrant pain and nausea, which led to a preliminary diagnosis of appendicitis. Examination revealed a systolic blood pressure of 190, as well as albumin in the urine, and appendectomy was withheld. The patient was hospitalized in his home town for about a week then, and it was said that he had gross hematuria on one occasion. About two weeks later swelling in the face developed, and he was admitted to a different hospital. There, he received 23 transfusions of plasma and 5 of whole blood and was given corticotropin (ACTH) therapy, which was discontinued owing to a noticeable increase of edema. From then on until his admission here the edema progressed rapidly and he suffered from several episodes of vomiting and generalized convulsions.

On admission, the patient was a somewhat underdeveloped pale child who had massive generalized edema. The fundi showed macular stars, angiospasm, cotton-wool exudates, and hemorrhages. The heart was enlarged and showed a gallop rhythm and tachycardia. No murmurs were heard. The lungs were clear. The abdomen was markedly distended by ascitic fluid. The rest of the physical examination revealed no significant findings. The temperature was 98.6 F., pulse rate 140, respiratory rate 26, and blood pressure 196/120, right arm, reclining.

Repeated urine examinations showed acid specimens with specific gravity ranging from 1.007 to 1.017, albumin 2 to 3+, 1 to 12 red blood cells per high-power field, 2 to 4 white blood cells per high-power field, and 3 to 8 cellular casts per low-power field. Admission blood examination showed a hemoglobin of 12.2 gm., or 77%; red blood cell count of 3,700,000, and white blood cell count of 12,400, with a differential count of 81% polymorphonuclear leucocytes, 2% basophiles, 1% eosinophiles, 9% lymphocytes, and 7% monocytes. The admission nonprotein nitrogen was 83 mg. per 100 cc., and the plasma CO_2-combining power 19 vol. %. The 24-hour endogenous creatinine clearance ranged from 8 to 18 liters (8 to 18% of normal for the patient's body size). The serum creatinine ranged from 2.0 to 4.8 mg. per 100 cc., and the blood urea nitrogen from 30 to 83 mg. per 100 cc. The total serum proteins were 3.7 gm., with serum albumin of 1.6 gm. per 100 cc.

On admission the patient was placed on a 200 mg. Na, 50 gm. protein, 2,000 Cal. diet. He was also given ammonium chloride as a diuretic. However it was found after five trials that NH_4Cl had failed to reduce the edema. He then received mercaptomerin injections three times weekly, and this caused a great reduction of the edema as well as amelioration of symptoms. His weight dropped from 133 lb. (60 kg.) on admission to 93 lb. (42 kg.) on discharge two and one-half months later. He went home on the same diet that he had in the hospital and received mercaptomerin injections three times weekly.

About five weeks prior to the second admission on March 13, 1951, the patient complained of severe persistent pain in the right upper quadrant of the abdomen. Concomitantly, he complained of dyspnea, which gradually progressed to orthopnea. There was no recurrence of edema. During this admission the patient was acutely ill, complaining of abdominal pain and difficulty of breathing. The heart findings were essentially the same as during the first admission; there were coarse moist rales over both lung bases. There was marked tenderness over the right upper abdominal quadrant. Gross edema was not demonstrable in the extremities. The temperature was 100.8 F., pulse rate 140, and respiration rate 36. Blood pressure recorded from the right arm in the reclining position was 180/100. The hemoglobin was 6.0 gm. per 100 cc., and the red cell count was 1,610,000 per cubic millimeter. The total and differential white cell counts were normal. The patient rapidly got worse and died six hours after admission.

Autopsy revealed chronic glomerulonephritis, pulmonary edema, and a moderately enlarged heart which revealed marked atherosclerosis of both the left anterior descending and the posterior circumflex coronary arteries.

Patient H. K. is a 56-year-old white man who has had known heart disease following rheumatic fever 25 years ago. For the past five years he has suffered from congestive heart failure for

which he has been digitalized. Over the past year, edema became gradually worse and the ascites progressed to a degree that caused respiratory embarrassment. For these reasons he first sought admission to the University Hospital on Aug. 18, 1950.

Physical examination on admission showed marked orthopnea and a greatly enlarged abdomen. The temperature was 97.5 F.; pulse rate was 76 per minute and was markedly irregular, and the respiratory rate was 28 per minute. The blood pressure was 135/75, right arm, reclining. Engorgement of the neck veins was marked. Examination of the chest revealed signs of fluid at both lung bases. The heart was enlarged, the left border of dullness being in the sixth intercostal space in the anterior axillary line. The apical rate was 90, and the heart sounds were irregular. There was noted a pulse deficit of about 14 beats per minute. Systolic murmurs were heard at the aortic and pulmonic areas, and at the apex there were both systolic and late diastolic murmurs. The abdomen was greatly distended with fluid, and the liver margin was about four fingerbreadths below the right costal margin, as determined by percussion. There was marked edema of the legs, thighs, sacrum, scrotum, and both forearms.

Repeated urinalyses revealed no abnormal findings. The hemoglobin was 13 gm. and the red blood count 4,900,000 per cubic millimeter. The total white cell and differential counts were normal. There was no abnormality of liver function that could be detected by laboratory tests. The total serum proteins were 5.6 gm. per 100 cc., with serum albumin of 3.7 gm., globulin of 1.9 gm., and an albumin-globulin ratio of 1.9. Serum sodium was 138 mEq. per liter, plasma chloride 89 mEq. per liter. The patient weighed 157½ lb. (71 kg.) on admission.

On a program of 200 mg. sodium diet, ammonium chloride 3 gm. three times daily for three days on and three days off, and 2 cc. of mercaptomerin every three days the patient lost only about 3 lb. (1.3 kg.). Subsequently, a paracentesis was performed, with the removal of about 3 liters of fluid. Following paracentesis the weight fell from 154½ lb. (69.5 kg.) to 146 lb. (65.7 kg.). There were a definite clinical improvement and a gradual weight loss thereafter down to a level, at the time of discharge, of about 139 lb. (62.5 kg.). On a program of dehydration, the patient lost about 9 lb. (4 kg.) in three days but he did not excrete sodium, and when he was allowed to take liberal amounts of water he immediately regained the previous weight of 139 lb. (62.5 kg.).

The patient has subsequently been hospitalized three times since his first admission. Each time he complained of orthopnea and the accumulation of large amounts of abdominal fluid. On the last admission, thoracentesis produced 1,400 cc. from the right pleural cavity. The patient has confessed that he does not follow strictly the low sodium diet prescribed for him. Paracentesis was successful in removing large amounts of ascitic fluid during each admission. He is presently on a program of low sodium diet, injections of meralluride (Mercuhydrin) when needed, a mixture of ammonium and potassium carboxylic exchange resins (Resodec) 15 gm. three times a day every day and digitoxin 0.1 mg. every day and has remained fairly comfortable, although edema persists.

ACTIVE CHRONIC PULMONARY HISTOPLASMOSIS

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SEVERAL reports of single cases of chronic pulmonary histoplasmosis were published following the first cases described by Bunnell and Furcolow [1] and by Johnson and Batson [2] in 1948. Each case was thought to be exceptional, and this clinical type of histoplasmosis was not described as a separate clinical type by reviewers. When four cases with manifestations consistent with the term "active chronic pulmonary histoplasmosis" were recognized by us in three years, the experience suggested that this clinical form of histoplasmosis is relatively frequent under the conditions of our practice. During this same period only three cases of generalized histoplasmosis of the clinical types most frequently reported by others were recognized. The major clinical manifestations of seven cases of chronic pulmonary histoplasmosis previously reported and the major clinical manifestations of four new cases to be reported below have been compared to provide a composite clinical description of this active but benign type of the disease. Diagnostic methods and treatment are also described.

No recent tabulation of all the reported histoplasmosis cases is available, but a brief review of an unpublished tabulation of 138 cases was summarized by Hodgson, Weed, and Clagett in 1950.[3] In 65 of those cases there was reported to be pulmonary involvement. The principle types of pulmonary involvement were asymptomatic calcifications, asymptomatic chronic pulmonary infiltrations, acute pulmonary infections, and, finally, pulmonary infections incidental to a fatal, progressive, systemic disease. A total of seven reported cases of active chronic pulmonary histoplasmosis were found by reference to the tabulations of Meleney,[4] of Parsons

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1. Bunnell, I. L., and Furcolow, M.: A Report on 10 Proven Cases of Histoplasmosis, Pub. Health Rep. **63**:299-315, 1948.

2. Johnson, H. E., and Batson, R.: Benign Pulmonary Histoplasmosis: A Case Report with Brief Review of Literature, Dis. Chest **14**:517, 1948.

3. Hodgson, C. H.; Weed, L. A., and Clagett, O. T.: Pulmonary Histoplasmosis: Summary of Data on Reported Cases and Report of 2 Cases Treated by Lobectomy, J. A. M. A. **145**:807-810, 1951.

4. Meleney, H. E.: Histoplasmosis (Reticulo-Endothelial Cytomycosis): A Review, Am. J. Trop. Med. **20**:603-616, 1940.

and Zarafonetis,[5] and of Ziegler[6] and from a review of more recent case reports. These cases are entirely comparable to those to be described from our own experience and will be tabulated below. The criteria used in the selection of these reports from the literature were derived from the data obtained from our own cases. The following characteristics were emphasized: (1) the presence of a pulmonary lesion demonstrated by roentgenograms; (2) demonstration of Histoplasma capsulatum by culture in pulmonary tissue removed at operation or on repeated examination of the sputum[7]; (3) signs of activity of the disease, and (4) a chronic course. As long as the pulmonary lesion was the major manifestation and the course was chronic and the above criteria were met, the presence of extrapulmonary lesions or signs of generalization of the infection were not considered to prevent classification of the cases as chronic pulmonary histoplasmosis.

Our observations were made in a general hospital for veterans, of 1,250 beds, located in western Tennessee, about 10 miles from the Mississippi River. Patients entered the hospital from Tennessee and several nearby states, Arkansas, Alabama, Mississippi, Louisiana, and Missouri, and occasionally came from greater distances. Several reports of skin tests of residents of this area showed that in parts of this area there is a high incidence of positive skin reactions to histoplasmin.[8] Some of the cases would not have been recognized without surgical intervention and the resulting opportunity for mycologic examinations of tissues by one of us (E. U.), and in such cases the diagnosis certainly could not have been made in as definitive a manner by any other means. Some of these cases have been reported by Hughes and others.[9] Summaries of the records of the four patients whom we have seen follow.

REPORT OF CASES

CASE 1.—E. B., a 53-year-old white male farmer from Lawrence County, Ala., 30 miles (48 km.) from the Tennessee River, entered the hospital April 12, 1950, with the complaint of periodic postprandial subxiphoid distress, relieved by food and milk, of 20 years' duration. He gave a history of frequent chest colds with cough and production of yellowish sputum and occasionally noticed left upper anterior chest pain aggravated by deep inspiration. He lost 25 lb. (11.75 kg.) in six years. Twenty years previously he was told he had pulmonary tuberculosis, and the sputum was said to have been positive for acid-fast bacilli at that time.

Physical examination revealed a slender white man who appeared chronically ill. The anteroposterior diameter of the chest was increased, and there was mild epigastric tenderness. The erythrocyte count was 4,200,000 per cubic millimeter of blood and the hemoglobin estimation showed 13.6 gm. per 100 cc. of blood. The leucocyte count was normal. The erythrocyte sedimentation rate (Wintrobe method) was 16 mm. in an hour. Results of urinalysis were within normal limits, and serologic tests for syphilis were negative. Chest films showed accentuation of the left hilar shadow, with radiating fibrous strands extending from its upper pole to the upper field of the left lung, where band-like infiltrations were seen; there was a small density in the anterior portion of the right fifth rib, thought to represent a bone island.

5. Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in Man, Arch. Int. Med. **75**:1-23, 1945.

6. Ziegler, E. E.: Histoplasmosis of Darling: Review and Case Report with Autopsy, Ann. Int. Med. **24**:1073-1087, 1946.

7. Miss Elizabeth Ulrich, Medical Technician, performed the mycologic examinations.

8. Christie, A., and Peterson, J. C.: Histoplasmin Sensitivity, Am. J. Pediat. **29**:417-432, 1946. Palmer, C. E.: Geographic Influences in Sensitivity to Histoplasmin Among Student Nurses, Pub. Health Rep. **61**:475-487, 1946. Loosli, C. G.; Beadenkopf, W. L.; Rice, F. A., and Savage, L. J.: Epidemiological Aspects of Histoplasmin, Tuberculin and Coccidioidin Sensitivity, Am. J. Hyg. **53**:33-57, 1951.

9. Hughes, F. A.; Whitaker, H. W.; Lowry, C. C.: Polk, J. W.; Foley, F. E., and Fox, J. R., Jr.: Resection for Mycotic Pulmonary Diseases, Dis. Chest, to be published.

Roentgenographic examinations of the upper gastrointestinal tract revealed no abnormality, and the subxiphoid distress disappeared with symptomatic measures. Bronchoscopy revealed redness of the entire bronchial mucosa. Three 24-hour sputum specimens were negative on smear and culture for acid-fast bacilli. The patient was discharged on May 18, 1950.

About 10 months later, on March 28, 1951, he returned to the hospital, complaining of frequent respiratory infections with cough, sputum production, and left upper chest pain, and he reported that his local physician stated that there was persistence of pulmonary infiltration in roentgenograms. There had been no fever, night sweats, or further weight loss. Physical examinati . and

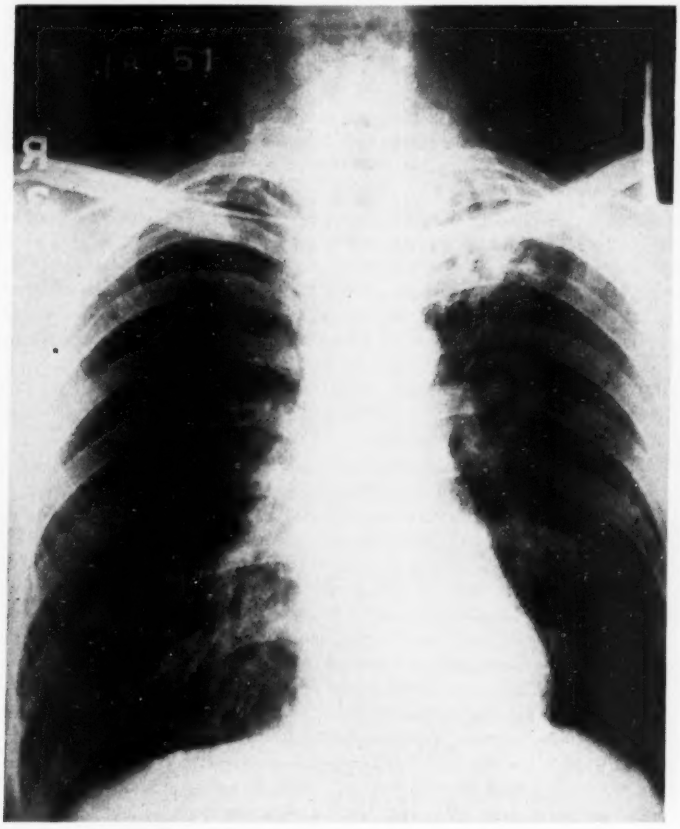

Fig. 1 (Case 1).—Roentgenogram of the thorax showing maximum pulmonary involvement. A mottled infiltration in the left upper lobe extends from the apex to the second rib anteriorly, and linear densities extend from the infiltration to the upper pole of the left hilum.

routine laboratory studies were unchanged. The erythrocyte sedimentation rate was 33 mm. in an hour. A roentgenogram of the chest on May 18, 1951 (Fig. 1), showed increased pulmonary involvement and a mottled infiltration in the upper lobe of the left lung, extending from the apex to the second rib anteriorly; linear densities extended from this infiltration to the upper pole of the left hilum. Within the infiltration several radiolucent areas were noted, suggesting cavitation. Oblique films of the chest revealed a cavity located posteriorly in the upper lobe of the left lung.

Eight sputum specimens and two gastric washings were negative on culture for acid-fast bacilli. Intracutaneous injection of 0.1 cc. of purified protein derivative of the tubercle bacillus

produced induration and erythema 1 cm. in diameter. The patient was afebrile and asymptomatic except for a moderate cough with scanty sputum. Bronchoscopy revealed no endobronchial disease. Segmental resection of the posterior apical segment of the upper lobe of the left lung was performed on May 21, 1951. Grossly the specimen showed a cavity 3 cm. in diameter surrounded by indurated and caseous areas. Microscopically the wall of the cavity consisted of necrotic debris and the surrounding lung parenchyma contained several large granulomata with central necrosis and zones of epithelioid cells, lymphocytes, and Langhan's giant cells. H. capsulatum was cultured from material from the cavity in the upper lobe, but the organism was not demonstrated on microscopic review of histologic sections. A thoracoplasty was done June 22, 1951, in which the entire second rib, the remaining portion of the third, and the posterior portion of the fourth were resected subperiosteally because of considerable retraction of the trachea. After recovery from surgical procedures the patient was afebrile, but moderate cough and production of sputum persisted. The erythrocyte sedimentation rate ranged from 15 to 20 mm. in an hour.

When last seen, 17 months after lobectomy, on Oct. 21, 1952, the patient felt well and was gaining weight, although moderate productive cough persisted. No signs of activity of the infection or the presence of localized or disseminated lesions of histoplasmosis were found on thorough examination.

Case 2.—P. G., a 45-year-old white male farmer, from Panola County, Miss., about 50 miles (80 km.) from the Mississippi River, entered the hospital April 22, 1951, because of hemoptysis on the day of admission. He gave a history of chronic cough with production of ½ to 1 oz. (14 to 28 gm.) of mucopurulent sputum per day for three years. He had hemoptysis on one previous occasion. A roentgenogram of the chest revealed mottled infiltration in the upper field of the left lung, extending from the apex to the second anterior rib. Skin test, using second strength purified protein derivative of tubercle bacilli, was positive. Three sputum specimens were negative microscopically and by culture for tubercle bacilli; bronchoscopy was negative; serial roentgenograms of the chest revealed no change, and the patient was discharged from the hospital about a month later, on May 31, 1951.

He returned to the hospital four months later, on Aug. 24, 1951, because of sharp left upper chest pain aggravated by movement and respiration, of three days' duration. The cough was unchanged, and the sputum was occasionally streaked with blood. Examination revealed the patient to be poorly nourished and chronically ill. Resonance was impaired over the left upper anterior chest, and harsh breath sounds were noted throughout both lung fields. The erythrocyte sedimentation rate (Wintrobe method) was 22 mm. in an hour. Total serum protein was 5.4 gm. per 100 ml. of blood. Serum albumin was 3.3 gm. and serum globulin was 2.1 gm. per 100 ml. of blood. Urinalysis showed no abnormalities, and serologic tests for syphilis were negative. A roentgenogram of the chest showed increased infiltration, with many radiolucent areas suggesting cavitation, which was later confirmed by planigrams.

The patient was thought to have pulmonary tuberculosis, but 12 sputum specimens were negative microscopically following concentration and on culture for tubercle bacilli. A sputum culture of Sept. 7, 1951, yielded H. capsulatum, and subsequently a total of 16 sputum cultures were positive for this organism through February 1952. When the presence of chronic pulmonary histoplasmosis was recognized, other foci and dissemination were sought but were not found. Bone marrow cultures were twice negative. Liver and skin biopsies were negative for fungi. Material from the gingival margin and purulent exudate from a left chronic otitis media were negative for fungi. Roentgenograms of long bones, spine, and skull showed no abnormalities. Proctoscopic examination showed no abnormalities. Intradermal tests using first strength purified protein derivative of tuberculosis were negative. Second strength purified protein derivative of the tubercle bacillus injected intradermally produced a reaction that was considered to be positive.

The patient's early hospital course was afebrile, but productive cough persisted and the sedimentation rate remained elevated, ranging from 15 to 52 mm. in an hour. Ethyl vanillate was given in two courses between Oct. 30, 1951, six months after first admission, and Jan. 14, 1952. The dosage was 788 gm. administered in 21 days and 1,804 gm. in 34 days, a total of 2,592 gm. in 55 days. This did not alter the clinical course, and the sputum remained positive for H.

capsulatum. The pulmonary infiltration in the upper field of the left lung increased slightly in size, as shown in the roentgenogram taken on Jan. 12, 1952 (Fig. 2). Therefore, left upper lobectomy and thoracoplasty were done on Feb. 18, 1952, ten months after the first admission. The resected lobe contained a cavity 3 by 2 by 5 cm. in diameter. The wall of the cavity showed granulomatous histologic reaction with large phagocytic macrophages and plasma cells. A nodular area from the parenchyma showed marked fibrosis and granulomatous reaction. No organisms were demonstrated histologically although culture from the cavity of the resected lobe yielded H. capsulatum. Postoperatively a faint infiltration in the upper lobe of the right lung developed

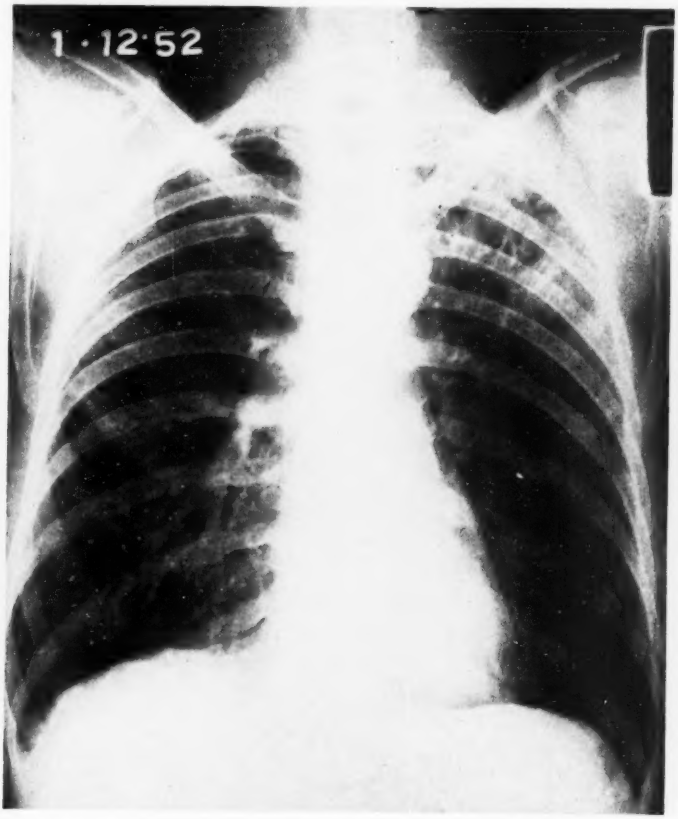

Fig. 2 (Case 2).—Roentgenogram of the thorax showing a mottled infiltration in the left upper lung field that extends from the apex to the second anterior rib.

and 2 of 14 sputum cultures yielded H. capsulatum, on March 26 and May 15, 1952, respectively. Productive cough persisted, and sedimentation rate ranged from 22 to 44 mm. in an hour. The patient was discharged June 11, 1952.

When he returned to the hospital on Aug. 15, 1952, no new symptoms were reported. A roentgenogram of the chest on Aug. 18, 1952, showed no change in the upper lobe infiltration in the right lung. Seven out of 13 sputum specimens and one of four gastric washings were positive on culture for H. capsulatum. Culture of the sternal bone marrow was again negative for fungi. *P*-aminosalicylic acid was given in a daily dose of 12 gm. for 25 days, beginning Sept. 11, because the spread of the infiltration suggested the possibility of tuberculosis. The

pulmonary infiltration did not change (Fig. 3) but was shown to be due to cavitary disease by planigram (Fig. 4). Stilbamidine was given intravenously daily for nine days, beginning Sept. 22, 1952, because of some reports of antifungal properties of this drug for H. capsulatum in vitro. Nineteen months after the first admission, on Nov. 18, 1952, a right upper lobectomy was done. The resected lobe contained a consolidated mass with a cystic central portion measuring 2.5 cm. in its greatest diameter. Section from this area showed dense scarring and lymphocytic infiltration. The organism could not be demonstrated on histologic section, but culture of resected lung tissue showed H. capsulatum. Postoperatively 10 sputum cultures were negative for fungi. The

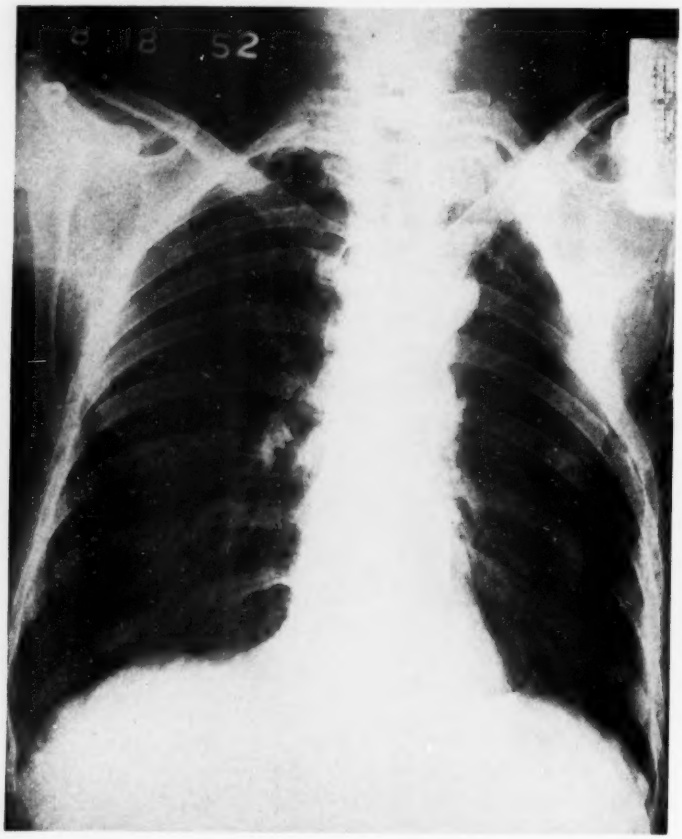

Fig. 3 (Case 2).—Roentgenogram of the thorax showing pulmonary involvement at the contralateral right apex that developed subsequent to the lesion shown in Figure 2. There are very fine mottled infiltrations and one radiolucency suggesting cavitation.

erythrocyte sedimentation rate remained elevated, ranging from 30 to 38 mm. in an hour. Postoperatively roentgenographs of the lungs were normal except for moderate postoperative reaction. During the course of the hospitalization, 30 sputum specimens and five gastric washing specimens were negative microscopically and by culture for tubercle bacilli. Cultures from resected lung tissue were also negative for tubercle bacilli. The patient was discharged home without evidence of disease Feb. 19, 1953, and was examined again and found to have no signs of recurrence on April 20, 1953, about five months postoperatively.

CASE 3.—C. W., a 43-year-old white male lead burner, from Clay County, Ark., about 60 miles (96 km.) from the Mississippi River, entered the hospital June 6, 1951. He became ill in August of 1947, when malaise and fatigability developed and he expectorated blood-streaked sputum. He was treated for malaria and improved, but fatigability and cough with occasional blood-streaked sputum continued. The diagnosis of pulmonary tuberculosis was made by chest x-ray in October 1948, and at that time the patient entered a tuberculosis sanitarium, where

Fig. 4 (Case 2).—Planigram of the right thorax made about the time of Figure 3, showing multiple cavities at the right apex.

he was hospitalized continuously until June 1949. Thereafter, he was examined at 90-day intervals, reentering the hospital in October 1950 because of evidence of spread. Pneumothorax was unsuccessful, and phrenicotomy was performed in November 1951. The patient was discharged in April 1951 and remained at home until May 1951, when he was admitted to another tuberculosis hospital because of radiographic evidence of spread. A course of penicillin and oxytetracycline (Terramycin) at that hospital resulted in marked decrease in sputum, and he was referred to this hospital with the diagnoses of arrested pulmonary tuberculosis and bronchiectasis. Of

several examinations of the sputum and gastric contents at these hospitals, only one specimen of gastric contents was positive on culture for acid-fast bacilli. Past history revealed that the patient had had a lesion of the lip excised in 1945, which he was told was a carcinoma.

Physical examination revealed a well-developed and well-nourished afebrile white man who did not appear acutely or chronically ill. There was a transverse surgical scar, 1 in. (2.5 cm.) in length, of the right anterior neck and a small vertical scar of the right lower lip. The lung fields were clear to auscultation and percussion. Admission hemogram revealed 5,050,000 red

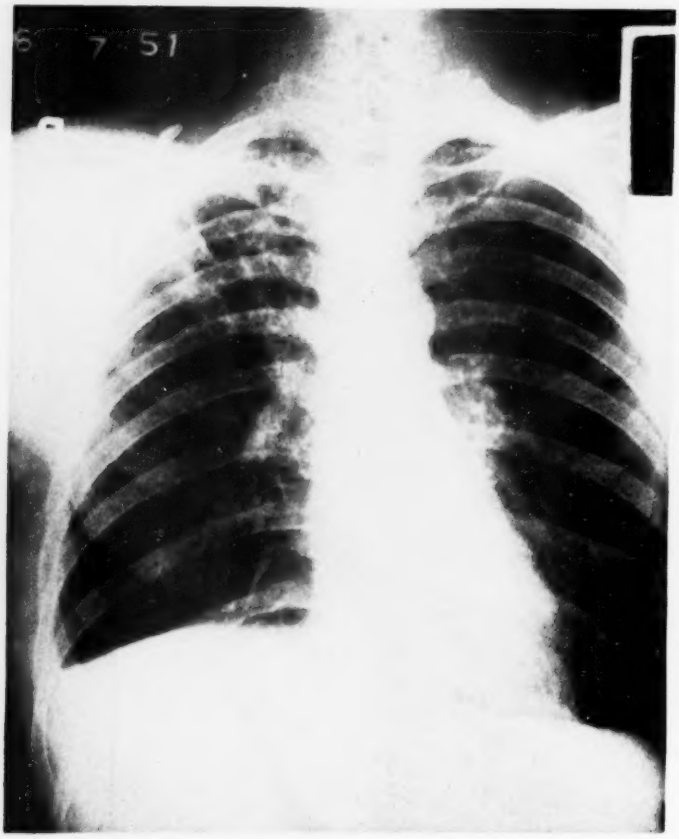

Fig. 5 (Case 3).—Roentgenogram of the thorax showing pulmonary involvement; there are mottled and linear infiltrations in the upper one-half of the right lung field, with several small radiolucent areas and a small infiltration in the left third anterior interspace.

blood cells, with 14.8 gm. hemoglobin per 100 cc., and 4,200 white blood cells, with 46% neutrophiles, 44% lymphocytes, 1% monocytes, and 9% eosinophiles. The erythrocyte sedimentation rate (Wintrobe method) was 35 mm. in an hour. Urinalysis showed no abnormalities, and serological tests for syphilis were negative. Roentgenogram of the chest on admission, June 7, 1951 (Fig. 5), revealed mottled and linear infiltration of the upper half of the right lung field, with several small radiolucent areas; there was a small density lying laterally in the left third anterior interspace.

Diagnosis on admission was pulmonary tuberculosis. One sputum specimen was negative on microscopic examination of concentrate and culture for tubercle bacilli. The patient's course was afebrile although moderate cough with expectoration of blood-streaked sputum continued. Bronchoscopy revealed no abnormalities, and results of bronchography were normal except for elevation of the main bronchus of the upper lobe of the right lung, probably secondary to atelectasis. A right upper lobectomy was done on Aug. 3, 1951, two months after admission. Grossly, the resected lobe exhibited a cystic cavity near the base, with many discrete shotty densities in the surrounding tissue. Microscopically, the wall of the cavity was lined by necrotic debris, beneath which was a zone of cellular fibrous tissue and chronic inflammation; the surrounding lung parenchyma showed marked scarring, peribronchial round cell infiltration, and round cell accumulations in some of the alveolar walls; there were scattered small tubercles with caseous centers and a surrounding zone of cellular fibrosis, lymphocytic infiltration, and a few giant cells. Culture from the resected right upper lobe was negative for tubercle bacilli, but culture for fungi showed H. capsulatum. The histologic specimen was then reexamined, and numerous macrophages containing small bodies resembling H. capsulatum were found. Postoperatively an empyema pocket at the right apex developed, for which thoracoplasty was done on Aug. 16, 1951.

A chest x-ray on Sept. 13, 1951, revealed an infiltration in the apex of the left lung, which had not been present on previous examinations. This was thought to represent a spread of histoplasmosis, but microscopic examination of six sputum specimens and 13 cultures of the sputum were negative for fungi. Purified protein derivative of tubercle bacilli first strength, 0.1 cc., produced a 4 cm. area of erythema with a 1 cm. area of induration. On Oct. 29, 1951, about four months after admission, ethyl vanillate was started, beginning with a daily dose of 12 gm., which was gradually increased to a maximal dose of 48 gm. on Nov. 9, 1951, which was then continued to Nov. 22, 1951. The patient received a total of 888 gm. in a 15-day period. Blood levels after the 10th day of therapy ranged from 12 to 21 mg. per 100 cc. On Nov. 20, 1951, hemoptysis developed, which persisted for four days. The possibility that disease in the upper lobe of the left lung represented activation of an old tuberculous infection was then considered, and the patient was given streptomycin, 2 gm. daily, and *p*-aminosalicylic acid, 3.0 gm. daily. Sputum cultures of Oct. 25 and 26, 1951, were reported positive for tubercle bacilli, and subsequently a total of 33 out of 44 sputum specimens were positive on microscopic examination of concentrate for tubercle bacilli and 21 of 31 sputum specimens were positive on culture for tubercle bacilli. The patient's further course was one of progressive disease. His illness was characterized by chronic cough with production of 1 to 2 oz. (28 to 57 gm.) of mucopurulent sputum a day; frequent hemoptysis, often of considerable degree; a long period of low-grade fever, and progressive weight loss. Serial roentgenograms showed increase in the upper lobe infiltrations in the left lung, with the development of a large cavity and extension to the left base. Streptomycin, *p*-aminosalicylic acid, pyrazinamide (aldinamide), isoniazid (isonicotinic acid hydrazide), and viomycin did not arrest the progress of the disease. On July 21, 1952, a perirectal abscess developed, and purulent drainage from the area persisted for five months after surgical drainage on July 22, 1952. One culture from this area for acid-fast bacilli and three cultures for fungi were negative. The patient was still confined to bed with a diagnosis of far advanced pulmonary tuberculosis 22 months after operation.

Case 4.—J. T., a 54-year-old white male cabinet maker, from Lee County, Miss., 115 miles (184 km.) from the Mississippi River, entered the hospital Nov. 26, 1951. In 1920 chronic cough developed and he had hemoptysis. He was told he had chronic bronchitis. Thereafter he had a chronic cough without sputum. In 1931 he had pneumonia. For the year prior to admission, cough was increased and he produced mucopurulent sputum. For one month before admission he had evening fever and left chest pain, aggravated by inspiration, and he produced from 1 to 2 oz. (28 to 57 gm.) of yellowish sputum daily. He lost 30 lb. (13.5 kg.) within a year preceding admission.

Physical examination revealed a slender white man who appeared chronically ill, with slight fever (temperature of 100 F.). Resonance was impaired and breath sounds were decreased over the left upper anterior chest. The liver and spleen were not palpable. The hemogram was within normal limits. The erythrocyte sedimentation rate (Wintrobe method) was 36 mm. in

an hour. Urinalysis showed no abnormalities, and serologic tests for syphilis were negative. A roentgenogram of the chest revealed mottled infiltration of the upper third of the left lung field, with many small radiolucent areas.

Initially it was thought that the patient had pulmonary tuberculosis, but one 24-hour and ten 72-hour sputum specimens were negative microscopically and on culture for tubercle bacilli. Early during hospitalization aqueous penicillin procaine was given in doses of 600,000 units per day for a three-day period, but the patient continued to have daily fever (temperature of 100 to

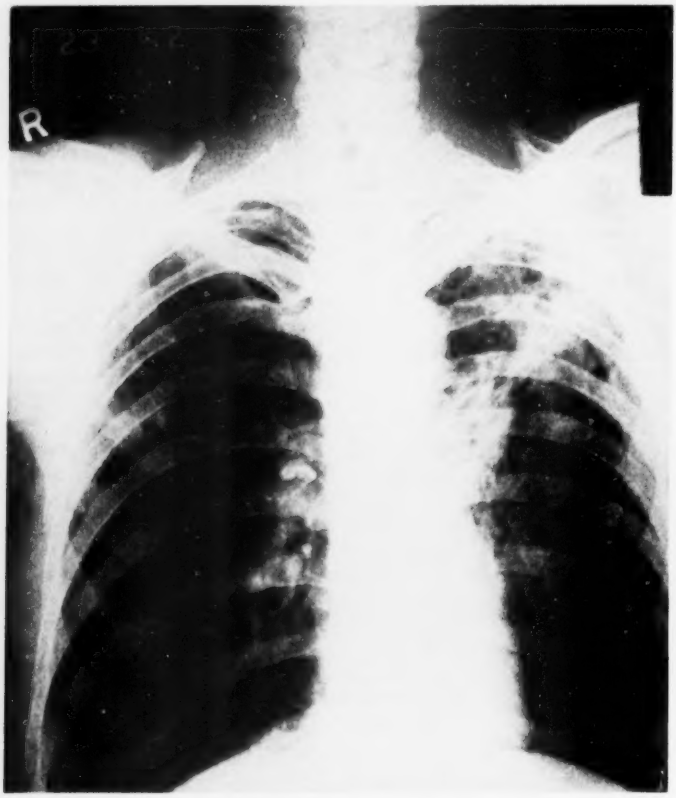

Fig. 6 (Case 4).—Roentgenogram of the thorax showing maximum pulmonary involvement; there is a mottled infiltration of the upper one-third of the left lung field, with many small radiolucent areas and small infiltrations in the left costophrenic angle and in the region of the right third rib anteriorly.

101 F.) for 17 days, after which he was afebrile. From Dec. 24, 1951, to Feb. 2, 1952, he received 1 gm. of streptomycin intramuscularly and 600,000 units aqueous penicillin procaine intramuscularly daily. A chest x-ray on Dec. 20, 1951, showed an increase in upper lobe infiltration in the left lung, but serial chest films thereafter revealed decrease to about the same appearance as seen at the initial examination, but on March 10 the infiltrate was denser, with extension toward the hilar region. Bronchoscopy on Dec. 12, 1951, and Feb. 6, 1952, revealed a creamy white purulent exudate draining from the left upper lobe bronchus. A sputum culture of Dec. 11, 1951, yielded H. capsulatum. Liver biopsy and bone marrow cultures were negative for tubercle bacilli and fungi. An intradermal test using 0.1 cc. of purified protein derivative of

tubercle bacillus containing 0.05 mg. second strength was positive. After becoming afebrile the patient felt well although mild cough with scanty sputum persisted. Exploratory thoracotomy was proposed to the patient but was refused, and he left the hospital without permission on March 18, 1952.

The patient returned to the hospital on Aug. 2, 1952, because a chest x-ray by his private physician showed increase in the pulmonary infiltration. He continued to feel well, and the cough was unchanged, but he had lost 5 lb. (2.25 kg.). Results of physical and laboratory examinations were essentially unchanged. The erythrocyte sedimentation rate was 34 mm. in an hour. A chest roentgenogram on Sept. 23, 1952 (Fig. 6) showed slight increase in upper lobe infiltration in the left lung. Small areas of infiltration appeared for the first time in the left costophrenic angle and in the region of the right third rib anteriorly. Planigrams of the chest revealed multiple large radiolucent areas in the apex of the left lung, thought to represent cavitation. First strength skin tests using purified protein derivative of tubercle bacilli were negative. During subsequent hospitalization, 13 of 13 sputum specimens and four of four gastric washings were positive on culture for H. capsulatum. In addition, the organism was found by direct examination of the sputum on six occasions attempted. Fifteen sputum specimens and seven gastric washings were negative on smear of concentrate and culture for acid-fast bacilli.

With the exception of one 10-day period of daily fever (temperature 99 to 100 F.) accompanied by increased cough and increased sputum the patient was afebrile. At other times 5 to 20 cc. of mucopurulent sputum were produced. The serial chest films showed no change in pulmonary infiltrations. From Sept. 22, 1952, to Nov. 5, 1952, the patient received 100 mg. isoniazid three times a day, without effect. Cycloheximide (Acti-dione) was started on Nov. 18, 1952, about a year after first admission, beginning with a dose of 20 mg. intravenously, and was increased to 60 mg. intravenously daily by the third day and then to 60 mg. intravenously twice daily by the seventh day, which dosage was then continued to Dec. 11, 1952. The patient received a total of 2,100 mg. in a 24-day period. A chest roentgenogram on Dec. 8, 1952, showed slight decrease in the size of the lesion in the left lung. A sputum specimen on Nov. 24, 1952, was positive for H. capsulatum. Further therapy and observation were not possible because the patient left the hospital for the Christmas holidays and did not return.

Tabulation of some of the data about the patients and their illnesses in Table 1 shows a general similarity among the several cases previously reported[10] and the four newly reported cases. The patients' ages ranged from 34 to 64. All were men except one. The duration of illness varied from 2 months in two cases to as long as 20 years in another. Six gave a history of illness of 12 months or less and the remaining five had more than one year's history of previous illness. The lesions were confined to the upper lung field in nine cases. In six cases, both right and left lungs were involved; in four only the right; and in one only the left. Nine of the pulmonary lesions were described as fibrocavitary in roentgenographic appearance, and three were also described as parenchymal in location. In one case the lesion was predominantly parenchymal in character and involved the whole of one

10. (*a*) Furcolow, M. L.: Further Observations in Histoplasmosis: Mycology and Bacteriology, Pub. Health Rep. **65**:965-994, 1950. (*b*) Hodgson, C. H.; Weed, L. A., and Clagett, O. T.: Pulmonary Histoplasmosis: Review of Published Cases and Report of Unusual Case, J. Thoracic Surg. **20**:97-104, 1950. (*c*) Bettag, O. L.: Pulmonary Resection for Histoplasmosis: A Case Report, ibid. **22**:434-438, 1951. (*d*) Wilson, H. M., and Duryea, A. W.: Pulmonary Histoplasmosis: Report of a Case Long Considered Tuberculosis Improved by Acti-Dione, Dis. Chest **21**:346-353, 1952. (*e*) Monroe, J., and Kurung, J. M.: Histoplasmosis: With Review of Literature and Report of a Case Proved by Culture, with Involvement of the Upper Lobe of Each Lung Simulating Active Bilateral Apical Tuberculosis, Ann. Int. Med. **38**:206-223, 1953. (*f*) Bunnell and Furcolow.[1] (*g*) Johnson and Batson.[2] (*h*) Hodgson, Weed, and Clagett.[3]

TABLE 1.—*Eleven Cases of Pulmonary Histoplasmosis Including Four Newly Reported Cases*

Reference	Age, Yr.	Sex	Race	Occupation	Duration When First Seen, Mo.	Pulmonary Lesion	Principal Symptoms	Treatment	Total Duration of Observation, Mo.	Outcome	Total Duration, Mo.
Footnotes 1 and 10*a*	52	M	W	Farmer	3½	Infiltration entire left lung and RUL	Cough, fatigue, recurrent fever, wt. loss	None	24	Progressive illness	27½
Footnotes 1 and 10*a*	64	M	W	Clerk	54	Bilateral apical infiltration; cavitary disease RUL	Sputum, cough, wt. loss	Bacillomycin, sulfadiazine	16	Death	70
Footnote 2	64	M	W	Farmer	10	Cavity, left apex; infiltration rt. upper and midlung fields	Cough, sputum, chest pain, wt. loss, fatigue	Bed rest, supportive	3½	Symptomatic improvement, x-ray unchanged	13½
Footnotes 3 and 10*b*	36	M	W	Carpenter	2	Grapefruit-size mass, RLL	Hemoptysis, fever, chest pain, wt. loss	Rt. lower lobectomy	24	Apparently well	26
Footnotes 3 and 10*c*	34	F	W	Housewife	17 6	Multilocular cavity, RUL	Cough, chest pain, fatigue	Penicillin, dihydrostreptomycin, chlortetracycline, RU lobectomy	9 29	No evidence of recurrence	35
Footnote 10*d*	51	M	W	Blacksmith	2 (31 yr.?)	Cavitary Dis., RUL	Cough, fever, chest pain, fatigue, wt. loss	RU lobectomy, cycloheximide	15	Recurrent bouts of fever responding tv cycloheximide, improved	17
Footnote 10*c*	56	M	W	Farmer, timber cutter, laborer, janitor	244	Infiltration, upper ½ each lung field, cavitation	Cough, sputum, chest pain, fever, wheezing, hemoptysis, fatigue, wt. loss	Penicillin, methdia-mer-sulfonamides	7	No change except 15 lb. (6.75 kg.) wt. gain	251
Present Case 1	53	M	W	Farmer	480	Fibrocavitary LUL	Cough, sputum, chest pain, wt. loss	LU lobectomy	30	Early favorable result, 17 mo.	534
Present Case 2	45	M	W	Farmer	36	Fibrocavitary LUL, later RUL	Cough, sputum, hemoptysis, chest pain	LU lobectomy, ethyl vanillate, RU lobectomy	22	Early favorable result, 5 mo.	58
Present Case 3	43	M	W	Lead burner	48	Fibrocavitary RUL	Cough, sputum, hemoptysis, fever	RU lobectomy, ethyl vanillate	23	Progressive tuberculosis	71
Present Case 4	54	M	W	Cabinet maker	12 (31 yr.?)	Fibrocavitary LUL, later RUL	Cough, sputum, fever, fatigue, wt. loss	Isoniazid, cycloheximide	13	Unchanged	25

lung. In another case, a well-demarcated rounded lesion suggesting a pulmonary neoplasm or granuloma was seen in the lower lobe of the right lung on roentgenographic examination.

The principle symptoms involved the respiratory system (Tables 1 and 2), usually cough, sometimes productive of thick purulent sputum, and in a few cases associated with small amounts of blood. About half of the patients had more active symptoms, such as fever and loss of weight and strength. Treatment was varied and will be described below. After periods of observation varying from 3½ months to 30 months, one patient died, five were unimproved, two were confined to bed

TABLE 2.—*Frequency of Symptoms in Eleven Cases of Chronic Pulmonary Histoplasmosis*

Symptom	Cases, No.
Cough	11
Weight loss	8
Expectoration (mucopurulent)	7
Chest pain	7
Fever	6
Fatigue	6
Hemoptysis	4
Wheezing	1

TABLE 3.—*Mycology and Mantoux Skin Tests in Eleven Cases of Chronic Pulmonary Histoplasmosis*

	Number of Cultures, Total/Positive				Mantoux (PPD) *		
					Positive		
Reference	Sputum	Gastric Washing	Bone Marrow	Resected Lung	0.0002	0.05	Negative
Footnotes 1 and 10*a*	19/6	3/0	...	...	1	..	0
Footnotes 1 and 10*a*	17/4	5/1	...	1/1	4	..	0
Footnote 2	1/1	...	...	...	0	0	1
Footnotes 3 and 10*b*	1/1	...	...	1/1	1	..	0
Footnotes 3 and 10*c*	10/6	3/0	...	1/1	..	..	2
Footnote 10*d*	20/7	...	...	1/1	..	..	..
Footnote 10*e*	7/7	...	...	...	0	2	0
Present Case 1	18/0	...	1/0	2/1	2	..	0
Present Case 2	53/25	4/1	2/0	2/2	..	2	0
Present Case 3	13/0	...	1/0	2/2	1	..	0
Present Case 4	14/14	4/4	1/0	...	..	2	0

* Purified protein derivative of the tubercle bacillus.

acutely ill, and three were apparently cured. The course of the illness was chronic and benign. The total period of illness varied from a minimum of 13½ months to 270 months. Three had been ill more than one year but less than three years when last seen. Four were ill from two to three years, and the remaining four were ill for four years and more.

Diagnosis of chronic active pulmonary histoplasmosis depends primarily upon (1) thinking of the possibility of the condition in patients with chronic pulmonary lesions of moderate severity and of long duration, especially after evidence for tuberculosis is sought and found absent, and (2) upon the use of specific diagnostic measures for identification of H. capsulatum. The results of such specific diagnostic methods are summarized in Table 3. Culture of the sputum for H. capsulatum was

repeatedly positive in 7 and positive at least once in 2 more of the 11 cases. In two cases sputum cultures were repeatedly negative, although H. capsulatum was found in cultures of resected pulmonary lesions. In the authors' patients with positive cultures of the sputum, direct microscopic examination of the sputum also showed characteristic tiny yeast-like micro-organisms intracellularly. This observation suggested the possibility that such direct microscopic examination of sputum for H. capsulatum should be carried out with greater frequency and that it might lead to a tentative but more prompt diagnosis of pulmonary histoplasmosis in some cases. Gastric washings were positive for three of five cases in which they were performed. In all three of these cases there were also positive cultures from the sputum. Bone marrow examinations were performed in the four cases reported by the authors and all showed negative cultures for H. capsulatum. Cultures of resected pulmonary lesions were positive in six cases. A skin reaction to protein of the tubercle bacillus was found in most of the cases of chronic pulmonary histoplasmosis. Five had positive reactions to purified protein derivative, first strength, and three to purified protein derivative, second strength. Two had negative reactions to both dilutions. In one case no skin tests were performed with purified protein derivative of tubercle bacillus. Serological tests and skin testing with antigens derived from H. capsulatum were performed in these cases. They have potential value in the diagnosis of chronic pulmonary histoplasmosis because of the high incidence of positive results, but they are both secondary in importance to the demonstration of the etiological agent, which was the basic procedure in this study, and they require more detailed tabulation and discussion than is possible at this time.

Despite the relatively benign course of chronic pulmonary histoplasmosis, the effects of therapy are disappointing. Medical therapy consisted primarily of various antibiotics and chemotherapeutic agents, both new and old, such as sulfadiazine, bacillomycin, penicillin, dihydrostreptomycin, chlortetracycline (aureomycin), cycloheximide, isoniazid, stilbamidine, and ethyl vanillate. All were employed without definite favorable effects. Further consideration will be given below to the results of ethyl vanillate therapy and to resection of the pulmonary lesion.

Ethyl vanillate was used systematically in the therapy of histoplasmosis and other mycotic diseases because of the report of Christie [11] of the recovery of 5 of 12 patients with the disseminated form of the disease. Two of the above patients with chronic pulmonary histoplasmosis (Cases 2 and 3) were treated with ethyl vanillate. Patient 2 received 2,592 gm. in 58 days, which resulted in a blood level of from 15 to 26 mg. per 100 ml. of blood. Patient 3 received 888 gm. in 15 days, which resulted in a blood level of 21 mg. per 100 ml. of blood. No improvement was manifested. Extension of the pulmonary lesions developed in Patient 2 during therapy and he was later treated surgically. Patient 3 was treated with ethyl vanillate after surgical therapy, but extension of the pulmonary infiltration, apparently due to coexisting pulmonary tuberculosis, developed during ethyl vanillate therapy. No further evidence of histoplasmosis was found, and it was believed that the symptoms and lesions were due to tuberculosis, in the special section of the Medical Service which undertook the further treatment of this patient.

11. Christie, A.; Middleton, J. G.; Peterson, J. C., and McVickar, D. L.: Treatment of Disseminated Histoplasmosis with Ethyl Vanillate, Pediatrics **7**:7-23, 1951; discussed, Am. J. Dis. Child **80**:874-877, 1950.

The treatment, course, and outcome in three patients with disseminated histoplasmosis seen during the same period proved valuable for comparison in judging the significance of the response to therapy of these patients with chronic pulmonary histoplasmosis. The first of these, H. C., a 46-year-old white male farmer, had ulcers of the mouth and tongue, hepatomegaly, and Addison's disease. H. capsulatum was recovered from mouth and bone marrow cultures. This patient improved while under treatment with ethyl vanillate and remained well under subsequent treatment for Addison's disease for three years of observation, up to the present. The dosage of ethyl vanillate was 465 gm. in 22 days, with blood levels of 17 mg. per 100 ml. Ethyl vanillate, therefore, was associated with arrest of the disseminated disease in this one case in our experience. The full significance of these observations will not be known until they have been confirmed by others or substantiated by treatment of a larger number of cases. The second patient with disseminated histoplasmosis, W. L., a 34-year-old Negro male service station attendant, showed hepatosplenomegaly and fever of unknown origin. H. capsulatum was recovered from the bone marrow on culture. No specific therapy was administered, but after a febrile course of seven days the patient went on to apparent complete recovery, maintained for one year. A third case of disseminated histoplasmosis, of D. L., a 56-year-old Negro male laborer, was recognized at postmortem examination as a terminal event in a patient under prolonged treatment for pulmonary tuberculosis. This man's course was similar to that in a large proportion of histoplasmosis cases reported in the literature that were recognized after generalized involvement occurred. It seems probable that the recognition of a greater proportion of cases during life, while the disease is localized in its distribution or generalized but mild in its manifestations, may result, as in this whole series of seven cases, in a change in our general conceptions of prognosis in histoplasmosis. Therapy undertaken in cases recognized while in the chronic state or while showing mild symptoms of acute disease must be judged in the light of the possibility that benign forms of histoplasmosis are more common than the cases reported in the past would lead one to believe.

Surgical treatment of chronic pulmonary histoplasmosis was described by Hughes and co-workers [9] for two of the cases reported in this study, Cases 1 and 3. Surgical treatment was used in a third case, Case 2, and will be reported at a later date by that author. It should be noted here that in Case 1 removal of unilateral pulmonary fibrocavitary disease resulted in freedom from symptoms for 17 months. In Case 3 removal of a fibrocavitary lesion of the apex of the right lung was followed by the appearance of a new lesion, at the apex of the left lung, which proved to be tuberculous, and there was a persistent subsequent downhill course despite treatment for tuberculosis. The result in this case emphasizes that pulmonary tuberculosis may be present simultaneously with histoplasmosis and that throughout the course of nontuberculous chronic pulmonary disease adqeuate precautions to recognize the second infection and adequate specific treatment should be maintained. Patient 2, treated surgically, was subjected to two consecutive lobectomies, one of each upper lobe, with reappearance of positive sputum cultures for H. capsulatum and spread to the opposite upper lobe after the first operation but with freedom from spread and negative sputum cultures for five months after the second operation. These results suggested the indications for surgical treatment; namely, a localized lesion

without evidence of tuberculosis. These results are similar to those reported by others in the Table above. Two cases (Hodgson, Weed, and Clagett [12] and Hodgson and others [13]) had successful outcomes, and in one case [10d] there was a relapse.

SUMMARY AND CONCLUSIONS

Comparison of case reports of seven cases selected from the literature and four new cases of chronic active pulmonary histoplasmosis discloses that the clinical manifestations tend to be uniform.

The infection is found among country dwellers in the Mississippi Valley who have symptoms of chronic cough, malaise, loss of weight, and fever for from a few months to several years. Roentgenographic examinations show lesions, usually in the upper lobes of the lungs, similar to those of chronic pulmonary tuberculosis, usually fibrocavitary in appearance. Specific examinations for evidence of tuberculosis usually yield negative results. Mycologic examination of sputum or biopsy material shows the presence of Histoplasma capsulatum.

Diagnosis depends primarily upon demonstration of H. capsulatum in resected pulmonary tissue or repeatedly in the sputum.

The course is benign and is not altered by medical therapy. Surgical excision of involved pulmonary tissue had early favorable results in two of three cases but further observation is necessary.

12. Hodgson, Weed, and Clagett.[3] Hodgson, Weed, and Clagett.[10b]

13. Hodgson, Weed, and Clagett.[3] Bettag.[10c]

Case Reports

BENIGN ASEPTIC MENINGITIS DUE TO LEPTOSPIRA GRIPPOTYPHOSA

Second Report of Clinical Infection in the United States

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THE SEVERAL pathogenic leptospira produce in man a group of closely related diseases. These infections have received considerable attention in Europe for many years. In the United States, leptospirosis has been identified almost exclusively with that due to Leptospira icterohaemorrhagiae (leptospiral jaundice, Weil's disease). It is becoming more obvious that other leptospiral disease is present. Several dozen cases of infection with Leptospira canicola (canicola fever),[1] several instances of infection with Leptospira pomona (swineherd's disease),[2] and an outbreak of disease attributed to Leptospira autumnalis (pretibial fever, Fort Bragg fever, autumnal fever)[3] have been noted in this country. In November, 1952, Spain and Howard[4] reported the first case of leptospirosis due to Leptospira grippotyphosa (mud fever) in the United States. Their patient had an icteric febrile illness. We are reporting a patient with an anicteric course marked by a benign aseptic meningitis. This is the second instance, to our knowledge, of leptospirosis due to Lept. grippotyphosa in the United States, and the clinical course is perhaps more typical of the infection as described elsewhere than is that of the case reported by Spain and Howard.

REPORT OF A CASE

L. E., a 25-year-old white airman, began to have intermittent left flank pain on July 6, 1952. On July 13, one week later, the pain became steady and severe. He began to have chills, fever, generalized aching, and frequent urination and was admitted to the urology service for observation. The physical findings were normal except for tenderness over the left renal area and a temperature of 103.6 F. The urine had a specific gravity of 1.030, was graded as 1 + for albumin, and on microscopic examination showed occasional white and red cells in each field. The leucocyte count was slightly elevated, to 16,000, with a differential cell count of 93% neutrophiles and 7% lymphocytes. The erythrocyte count was 4,620,000, and the hemoglobin 14 gm.

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1. Haunz, E. A., and Cardy, J. D.: Canicola Fever: Report of Nine Cases in One Family, with Abstract of the World Literature, A. M. A. Arch. Int. Med. **89**:978 (June) 1952.

2. Schaeffer, M.: Leptospiral Meningitis: Investigation of a Water-Borne Epidemic Due to L. Pomona, J. Clin. Invest. **30**:670 (June) 1951. Coffey, J. H.; Dravin, I., and Dine, W. C.: Swineherd's Disease (Aseptic Meningitis) Due to Leptospira Pomona, J. A. M. A. **147**:949 (Nov. 3) 1951. Beeson, P. B.; Hankey, D. D., and Cooper, C. F., Jr.: Leptospiral Iridocyclitis: Evidence of Human Infection with Leptospira Pomona in the United States, ibid. **145**:229 (Jan. 27) 1951.

3. Gochenour, W. S., Jr., and others: Leptospiral Etiology of Fort Bragg Fever, Pub. Health Rep. **67**:811 (Aug.) 1952.

4. Spain, R. S., and Howard, G. T.: Leptospirosis Due to Leptospira Grippotyphosa: First Report of Occurrence in United States, J. A. M. A. **150**:1010 (Nov. 8) 1952.

The patient was admitted as an emergency during the night and received 250,000 units of penicillin and 1.0 gm. of aureomycin by order of the duty officer after a urine culture was obtained. On the following morning the temperature was only 100 F., and additional antibiotics were withheld pending further study. Subsequent urine specimens were normal, the urine cultures were negative for pathogens, and intravenous pyelography showed no abnormalities. Blood urea nitrogen on admission was 19.2 mg. per 100 cc., a slightly high value in our laboratory, but was found to be 16.3 mg. two days later. No further treatment seemed indicated. The patient was afebrile and asymptomatic on the second hospital day and was discharged on the fourth day with a diagnosis of acute left pyelonephritis.

On the day after discharge, 12 days after the initial symptoms, the airman noted a mild bilateral frontal headache. This became progressively more severe and failed to respond to self-treatment with ice packs and acetylsalicylic acid (Aspirin) at home. On July 21, 1952, three days later, the patient was again admitted to the hospital. He was again seen as an emergency by the same duty officer as before. On this occasion there was no flank tenderness and no history of urinary symptoms, nor were there any gastrointestinal symptoms of nausea, vomiting, or diarrhea. The examination disclosed a temperature of 100 F. and a moderately stiff neck, with complaint of pain in the neck and back on attempted anteflexion of the head. There were no other abnormal physical findings. Poliomyelitis being prevalant in the area at the time, an admission diagnosis of this disease was recorded, and the patient was admitted to the poliomyelitis ward on the medical service.

The medical history as obtained on the poliomyelitis ward contributes little to an investigation of the origin of the leptospirosis, and the airman was no longer available for further questioning when the true diagnosis became apparent. The man was a student in a technical school, had been in the Air Force for eight months, had never been out of the United States, and was not known to have had any previous illness. There is no specific history regarding animal or contaminated water contacts.

Urinalysis and hematology studies showed no abnormalities and serological test for syphilis was negative on the second admission. The spinal fluid was examined on admission and at the end of the first and second weeks. All pressures were less than 16.0 cm. water, and the dynamics were normal. The initial cell count was 280, the second 98, and the last 21 per cubic millimeter. Lymphocytes only were present on all counts. The initial spinal fluid protein was 101.75 mg. and the final determination 64.8 mg. per 100 cc. Tests for sugar and Kahn tests were negative, culture yielded no pathogens, and the colloidal gold curves were negative on all specimens.

For the first five days of the second hospitalization a low grade fever (100 F.) was noted. As this disappeared, the subjective and objective findings returned to normal. Other than the fever and stiff neck, no abnormalities were present on the general physical examination or on the neurological examination at any time during the hospital stay. The patient was discharged on the 18th hospital day, afebrile and asymptomatic, having received only symptomatic therapy.

Some nonparalytic disease was present in the epidemic of poliomyelitis which was occurring throughout the area at the time this case appeared. In five such cases in our poliomyelitis ward, where the diagnosis was probable but not absolute, serological studies were requested. In this particular case the spinal fluid protein was somewhat higher than expected and lymphocytes only had been noted in the fluid. The serological studies in this instance established the disease process as leptospirosis due to Lept. grippotyphosa some six weeks after the patient was discharged from the hospital as having a case of nonparalytic poliomyelitis.

Serological Studies.—The serological examinations were conducted by the veterinary division of the Army Medical Service Graduate School, Army Medical Center, Washington 12, D. C. Serum specimens were obtained on July 31, Aug. 19, and Aug. 30, 1952, the 39th, 58th, and 69th days after onset of the flank pain. Complement-fixing antibodies for lymphocytic choriomeningitis and for mumps were absent. The specimen of July 31 showed a microscopic agglutination titer for leptospirosis of 1:6400, and the specimen of Aug. 30 a titer of 1:1600. These sera were examined by the agglutination lysis technic of Schuffner and Mochtar, employing live antigens. The specimen drawn July 31 was used for agglutination absorption studies, living cultures being employed. The absorption of this sera with type strain Lept.

grippotyphosa, Moscow V, removed all agglutinating antibodies, indicating this to be a specific reaction. This is the first instance in which definitive absorption studies have been conducted on a human infection of this type in the United States.[5]

COMMENT

Leptospirosis grippotyphosa, also known as mud fever, swamp fever, slime fever, harvest fever, field fever, and schlamfieber, is normally one of the milder leptospiroses.[6] The onset is characteristically sudden, with headache, chills, pains in the back and legs, and sometimes nausea, vomiting, and diarrhea. Jaundice is uncommon. A macular rash appears on the face and body in a minority of cases on the third or fourth day. The disease is self-limited, the temperature falling gradually, and lasts for five to seven days. A short relapse may occur several days later.

In leptospiral infections other than Weil's disease[7] jaundice is uncommon (15%). Meningeal irritation is common and may be a dominant feature in some cases. Renal involvement, usually transient, is also common.

The clinical picture in this case corresponds closely in symptoms and severity to the disease as observed in Europe. The history contributes nothing to the epidemiology of the condition, whose animal reservoir in this country is unkown.[7] Elsewhere, infected rodents (voles, field mice) have been found.[4] Lept. pomona, endemic in swine and cattle, has been identified in farm animals in five counties which almost surround this base[8]—the significance of this in considering the possible distribution of other leptospira in the area is purely speculative.

The pattern of leptospiral infection in the United States has probably been obscured by the dominant interest in the more severe Weil's disease and by a dearth of diagnostic facilities for the milder leptospiroses until recently.[9] In a deliberate search, Beeson and Hankey[10] were able to demonstrate leptospiral causation for 9 of 35 cases of benign aseptic meningitis in a short period of time, and Haunz and Cardy[1] identified nine cases of canicola fever in one family. On the other hand, only eight cases of Weil's disease and none of the other human forms of leptospirosis are noted in the records of the Department of Public Health of the State of Illinois in the past 10 years.[11] The index of suspicion for leptospiral infections is already high among epidemiologists, and more reports will appear as clinicians become more aware of the diseases.

The diagnosis of leptospiral disease rests on serological confirmation of a clinical suspicion.[6a] A new and comparatively simple complement-fixation test is becoming available and should facilitate diagnosis of the diseases.[7] The manifestations of

5. Yager, R. H.: Personal communication to the author.

6. (*a*) Wilson, G. S., and Miles, A. A., in Topley, W. W. C., and Wilson, G. S.: Topley and Wilson's Principles of Bacteriology and Immunity, Ed. 3, Baltimore, Williams & Wilkins Company, 1946, pp. 1836-1837. (*b*) Buckland, F. E., and Stuart, R. D.: Mud Fever (Leptospirosis) in the British Army in France, Lancet **2**:331 (Sept. 15) 1945.

7. Leptospirosis in Man and Animals, Editorial, J. A. M. A. **150**:1406 (Dec. 6) 1952.

8. Davenport, L. R.: Swineherd's Disease, Weekly Report, Division of Preventive Medicine, Illinois Department of Public Health, Aug. 16, 1952.

9. Sacks, M. S.: The Problem of Leptospirosis, Ann. Int. Med. **33**:481 (Aug.) 1950.

10. Beeson, P. B., and Hankey, D D.: Leptospiral Meningitis, A. M. A. Arch. Int. Med. **89**:575 (April) 1952.

11. Schuman, L. M.: Personal communication to the author.

leptospiral infection are protean and may suggest hepatic, renal, ocular, dermatological, or meningitic disease or a typhoid-like febrile illness. With the normal mild course, self-limited nature, and low mortality rate (exclusive of Weil's disease) of these diseases, the diagnoses will likely be made in retrospect in most cases, since the rising agglutination titer, the most reliable diagnostic test, requires two to eight weeks to reach maximum.

SUMMARY

Leptospira grippotyphosa was identified as the causative agent in a case of benign aseptic meningitis. This is believed to be the second case of clinical infection with this organism in the United States and the first in which definitive absorption studies were done on sera. The disease in this patient closely approximated the syndrome described as occurring elsewhere in the world. With increased interest and improving diagnostic facilities it is expected that further cases of this and other leptospiroses will be recognized more frequently in this country.

Case Reports

MALIGNANT HYPERTENSION IN A PATIENT WITH RENAL ARTERY OCCLUSIONS

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GOLDBLATT [1] and Wilson and Byrom [2] have shown experimentally that occlusion of renal arteries in animals results in sustained hypertension. Yuile [3] reviewed the relation of obstructive lesions of the main renal arteries to hypertension in man and concluded that in only a small percentage of the reported cases could a definite etiologic relationship be established between the vascular lesion and the elevation of blood pressure.

This report is concerned with the unusual case of a young woman with a documented long history of normotension who died from the sequelae of a short course of malignant hypertension associated with recent thrombotic unilateral renal artery occlusion. The concurrent onset of malignant hypertension and complete occlusion of a renal artery strongly suggests an etiologic relationship.

REPORT OF A CASE

M. A., a 32-year-old white woman, was admitted to Montefiore Hospital on Jan. 26, 1952, because of severe abdominal pain, sudden blindness, and hypertension. Approximately nine weeks previously abdominal pain had developed, usually appearing after she had eaten. Examination on Nov. 21, 1951, revealed mild tenderness in the epigastrium and both upper quadrants. The blood pressure was 125/86 mm. Hg. The pain recurred intermittently for the next two months. A severe episode of abdominal pain only partially relieved by meperidine (Demerol) occurred on Jan. 21, 1952. Examination on Jan. 23 revealed pain and tenderness to the right of the umbilicus. The patient exhibited bizarre behavior, with inability to concentrate, depression, and crying spells. The urine was free from sugar and albumin; microscopic examination was not done. On Jan. 25 the patient suddenly became blind and suffered from nausea and retching. For the first time, examination revealed hypertension, with a blood pressure of 180/120. The patient gradually became disoriented, lethargic, and incontinent of urine. Stiffness of the neck developed on Jan. 26, the day of admission.

The patient had a history of hay fever and occasional hives for many years. In 1946, during a pregnancy, "pleurisy," followed by phlebitis developed. She had seven miscarriages after 1943, all in the second and third month of pregnancy. Examination of the fetuses never revealed evidence of syphilis.

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1. Goldblatt, H.: Renal Origin of Hypertension, American Lecture Series, No. 14, American Lectures in Pathology, Springfield, Ill., Charles C Thomas, 1948, pp. 15-50.

2. Wilson, C., and Byrom, F. B.: Renal Changes in Malignant Hypertension: Experimental Evidence, Lancet **1**:136-139 (Jan.) 1939.

3. Yuile, C. L.: Obstructive Lesions of Main Renal Artery in Relation to Hypertension. Am. J. M. Sc. **207**:394-404 (March) 1944.

The patient's serological reports have been conflicting. Repeated tests from 1942 to 1948 gave negative, doubtful, or positive reactions. The same specimen gave a positive Kahn and a negative Wassermann reaction in 1948, when the spinal fluid Wassermann reaction was negative and the colloidal gold curve was 0000000000. The Mazzini and Kolmer tests were reported as 2 + in 1949.

In 1949 the patient had pain and swelling of the left lower extremity, which abated spontaneously, only to be followed by a thrombophlebitis of the deep veins of the right lower extremity, for which she was admitted to Montefiore Hospital on June 27, 1949, when the following findings were noted: a mild hypochromic anemia, a normal urinalysis, and a blood pressure reading of 120/70.

She had been examined seven times by one of us from July, 1949 to November, 1951. Blood pressure readings taken six times ranged from 114 to 120 mm. Hg systolic, and 80 mm. diastolic.

On admission to the hospital the patient was disoriented and restless. She had a stiff neck, with positive Kernig and Brudzinski signs. The temperature was 102 F. and shortly rose to 104 F. The blood pressure was 180/95. After a generalized convulsion, one hour after admission, the blood pressure rose to 210/100.

Examination of the mouth revealed a lacerated tongue. The chest was clear to percussion and auscultation. The heart was not enlarged; there was a soft apical systolic murmur. The apical heart rate equaled the pulse rate and was 120 per minute. There were no abdominal masses. The pupils reacted to light. The fundi could not be visualized because of the patient's extreme restlessness. The right eyelid dropped. There was an internal strabismus of the right eye. There was generalized hyperreflexia, with bilateral ankle clonus and a right Babinski sign.

On several determinations, the white blood cell count varied between 22,000 and 31,000 per cubic millimeter, with approximately 90% polymorphonuclear leucocytes; the hemoglobin varied between 11 and 14 gm. per 100 cc. Analysis of catheterized urine specimens on Jan. 28 and 29 revealed a specific gravity of 1.010, a negative reaction for sugar, 3 + reaction for albumin, several crenated and fresh red blood cells, hyaline and granular casts, and occasional white blood cells. On the day of the patient's death, while she was receiving dextrose infusions, the urinalysis showed a specific gravity of 1.030, a 4 + reaction for albumin, a 3 + reaction for glucose, many granular casts, and many red and white blood cells per high power field. On Jan. 28, the blood urea nitrogen was 24.8 mg. per 100 cc. and the CO_2 content 22 mEq., serum sodium 138 mEq., and serum potassium 4.0 mEq. per liter.

A lumbar puncture after the convulsion, one hour after admission, disclosed an initial pressure of 130 mm. water, with normal dynamics; the fluid, ground glass in appearance, contained 1,400 red blood cells and 50 polymorphonuclear leucocytes per cubic millimeter. A clinical diagnosis of bacterial meningitis was made. The patient was treated with penicillin and sulfadiazine. Within 24 hours the temperature dropped from 104 F. to 99 to 100 F., and the patient appeared to be improved. She awoke, spoke occasionally, and answered questions. The neck became less rigid. Cultures of the spinal fluid obtained prior to chemotherapy proved to be sterile. Spinal tap was repeated two days after admission. The initial pressure was 400 mm. of water, the final pressure 200 mm. of water. There were 400 fresh and partly crenated red blood cells per cubic millimeter. The spinal fluid sugar was 52 mg., the chlorides 404 mg., and the protein 134 mg. per 100 cc. On the third hospital day the patient became less responsive and thrashed about in bed. On the fourth hospital day she lapsed into a deep coma. At this time she had a stiff neck, bilateral Babinski signs, bilateral papilledema, and scattered retinal hemorrhages. The diagnosis was intracerebral hemorrhage; bilateral occipital burr holes were made. A sirupy reddish fluid was found in the right ventricle and clear, colorless fluid in the left. On the fourth hospital day, one hour after ventriculography was performed, the patient died.

The blood pressure was 206/100 on Jan. 26; 170/100 on Jan. 27; 182/104 on Jan. 28 and 190/110 on Jan. 29, 1952.

The final clinical diagnosis was intracranial hemorrhage, etiology unknown.

Autopsy Observations

Results of Gross Examination.—Heart: The heart weighed 250 gm. There was no dilatation or hypertrophy of any chamber. The wall of the left ventricle was 1.0 cm. and that of the right 0.4 cm. in thickness. All the valve rings and cusps were unremarkable. The aortic valve had delicate cusps, with no rolling of edges or separation of commissures. The aortic valve ring measured 8 cm. and was not dilated. The coronary ostia were patent and normal in size, shape, and position. There was no arteriosclerosis or narrowing of the coronary artery tree.

Aorta: The entire aorta was normal in circumference, thickness, and elasticity. The intimal surface was smooth and contained no atheromatous plaques, wrinkles, or crevices except for an irregularity at the level of the origin of the renal arteries. On the anterior wall of the aorta between the renal arteries was a firm elevated plaque measuring 2 by 1.5 cm., roughly pentagonal in shape (Figs. 1 *A* and 2 *A*). A finger-like extension of this plaque penetrated into the ostium of the left renal artery for a distance of 4 mm. and occluded approximately one-third of the lumen (Figs. 1 *B* and 2 *B*). This artery was otherwise unremarkable. The plaque extended 0.5 cm. into and appeared to occlude the right renal artery at its origin. Continuing from this extension to the kidney hilus was a soft red thrombus which entirely occluded the rest of the right renal artery (Figs. 1 *D* and 2 *D*).

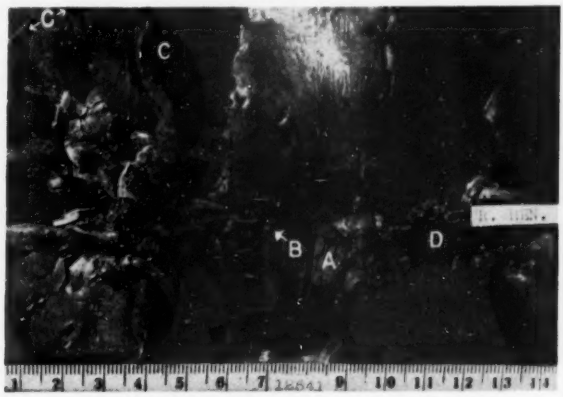


Fig. 1.—Elevated aortic plaque (*A*) between renal arteries, with extension (*B*) into ostium of left renal artery, and hemorrhages (*C*) in left kidney. There is a fresh thrombus (*D*) in the right renal artery and atrophy of the right kidney. This is a formalin-fixed specimen. Incision through the mesenteric orifices and plaque was made after death.

Kidneys: The right kidney was atrophied (Figs. 1 and 2). It weighed 50 gm. and measured 8 by 4 by 2 cm. The cortical surface after removal of the capsule was smooth. On cut section, the cortex measured 2 to 3 mm. in width and contained numerous yellow recent cortical infarcts (Fig. 2 *E*). The cortical striations and corticomedullary junctions were well demarcated. The left kidney weighed 120 gm. and measured 12 by 6 by 3 cm. Numerous irregular-sized fresh hemorrhages (Figs. 1 *C* and 2 *C*) were seen on the external and cut surfaces in the cortex and medulla. The cortex measured 4 to 6 mm. The cortical striations and corticomedullary junctions were well demarcated.

Brain: There were large fresh hemorrhages in the leptomeninges overlying the posterior parietal lobes 2 cm. anterior to the ventricular puncture wounds. The cerebellar tonsils were swollen, with molding about the medulla. After formalin fixation, sections revealed showers of petechiae in the midportion of the right parietal lobe and in the thalamic nuclei. Massive fresh hemorrhages were found in the white matter, with extensions into the gray matter of both occipital lobes involving the optic radiations. Another hemorrhage, measuring 2 by 1 cm., was seen in the right hemisphere of the cerebellum.

Stomach: Small areas of malacia were present in the fundus of the stomach.

Findings on Microscopic Examination.—Heart: No abnormalities were noted in the heart.

Aorta: A chronic mesaortitis was present at the level of the origin of the renal arteries. The adventitia was slightly thickened. Collections of lymphocytes were present but not often associated with arterioles. Capillaries were increased in number. A moderate number of small arterioles showed fibrinoid necrosis and thrombosis. Moderate numbers of lymphocytes in clumps and a few vasa vasorum were found in the outer two-thirds of the media. The mononuclear cells did not accompany the vasa vasorum (Fig. 3). Elastic and Van Gieson connective tissue stains showed disruption of musculoelastic tissue of the outer two-thirds of the media. These defects were not occupied by collagenous tissue or invaded by capillaries. Superimposed upon and integrated with the injured media was a thick band of collagenous material, which formed the base of the elevated thrombotic plaque. Hyaline lamellae intermixed with red blood cells, fibrin, and platelets were fused with the collagenous band. The mesaortitis, marked at the level of the renal arteries, diminished progressively in intensity 2 to 3 cm. above and below this region. Sections were taken through the ostia of the renal arteries. The papilla-like extension from the main aortic plaque (Figs. 1 *B* and 2 *B*) into the left renal artery ostium consisted of organized and organizing material similar to that of the aortic mural thrombus. The left renal artery was normal in thickness and caliber. The ostium of the right renal artery was completely occluded by organized thrombus except for two lumina (within the old thrombus) which were filled with fresh thrombi (Fig. 4). Five

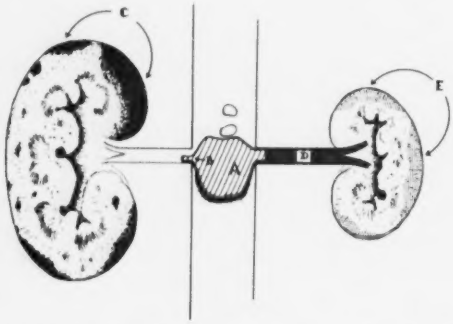


Fig. 2.—Diagrammatic drawing of photograph (Fig. 1). *A*, elevated aortic plaque; *B*, extension of plaque into ostium of left renal artery; *C*, hemorrhages in left kidney; *D*, thrombus in right renal artery; *E*, atrophy of right kidney, with cortical infarcts.

step sections of the right renal artery showed complete occlusion by fresh thrombus extending from the old thrombus to the hilus. In the hilus, the main branches of the renal artery were also occluded.

Kidneys: The right kidney showed marked changes of ischemic atrophy with interstitial fibrosis and tubular atrophy. The glomeruli were well formed and moderately hypercellular. Numerous fresh infarcts were present (Fig. 5). Some small arteries showed a hyaline intimal thickening similar to changes seen in atrophy of disuse. There was no evidence of arteriolonecrosis or arteriolosclerosis. The left kidney contained numerous small foci of interstitial hemorrhage in the parenchyma (Figs. 6 and 7 *C*). Small vessels (Fig. 6), including afferent arterioles (Fig. 7 *A*), were focally necrotic, as evidenced by smudged and thickened fibrinoid walls, karyorrhexis, and intramural hemorrhage. Glomeruli were congested and hypercellular, and many showed necrosis of capillary tufts (Fig. 7 *B*).

Brain: In the large occipital lobe hemorrhages were many macrophages and leucocytes, indicating an age of at least some days. There were scattered focal zones of cortical destruction which varied in age from weeks to months and a single fresh perivascular hemorrhage in the wall of the hypothalamus. Acute necrotizing arteritis was evident in some blood vessels in the infarcted foci. In other areas of the brain fibrinoid necrosis was present in a few vessels, and hyperplasia of intimal cells with hyaline thickening was noted in a moderate number of small vessels.

Adrenal Glands: Both adrenal glands contained focal areas of recent necrosis and hemorrhage in the cortex with extensions into the medulla. There was fibrinoid necrosis of the arterioles in the periadrenal fat. In the right adrenal gland there were old occlusions in the adrenal vein and smaller vessels.

Ovaries, Muscle, Lungs: There were fresh hemorrhages in the ovaries, gastrocnemius muscle, and subpleura of the lungs.

Eyes: The eyes revealed papilledema, round cell choroidal infiltrates, and sclerosis of the choroidal vessels.

Fig. 3.—Aortic thrombotic plaque superimposed upon mesaortitis. Mononuclear cell infiltration in media (*A*) and adventitia. Disruption of musculoelastic tissue of media. Hematoxylin and eosin; × 22.

Secondary Findings: In the gastrocnemius muscle there was an old well-organized phlebothrombosis. A few small pulmonary arteries were occluded by organized (old) emboli, some of which were recanalized. Malacia was noted in the fundus of the stomach.

Pathologic Diagnoses.—These were chronic mesaortitis; organizing mural thrombus in aorta with incomplete occlusion of renal arteries, atrophy of right kidney, complete occlusion of right renal artery by fresh thrombus, and multiple fresh infarcts of right kidney; arteriolonecrosis in left kidney, adrenal glands, brain, and adventitia of aorta; fresh hemorrhages and foci of necrosis in left kidney, occipital lobes of brain (massive), and adrenals; fresh hemorrhages in cerebellum, hypothalamus, lungs, muscles, and ovaries; foci of old malacia in cerebral cortex.

Secondary findings were organized thrombi in veins of calf muscle, organized pulmonary emboli, and gastromalacia.

Fig. 4.—*A*, extension of organized aortic plaque into right renal artery; *B*, fresh thrombi completely occluding lumina. Hematoxylin and eosin; × 19.

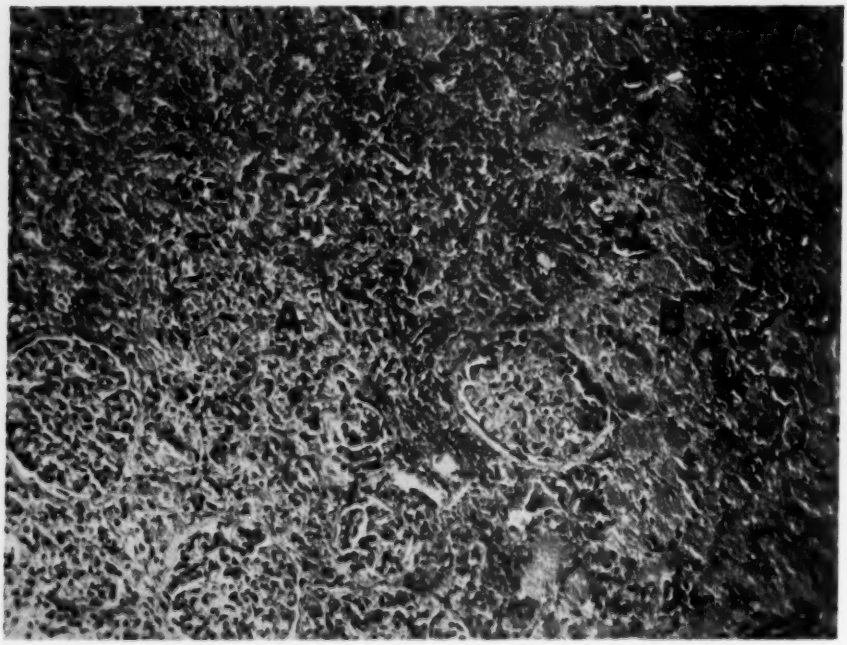


Fig. 5.—*A*, tubular atrophy and interstitial fibrosis in right kidney; *B*, infarct. There is no arteriolonecrosis. Hematoxylin and eosin; × 120.

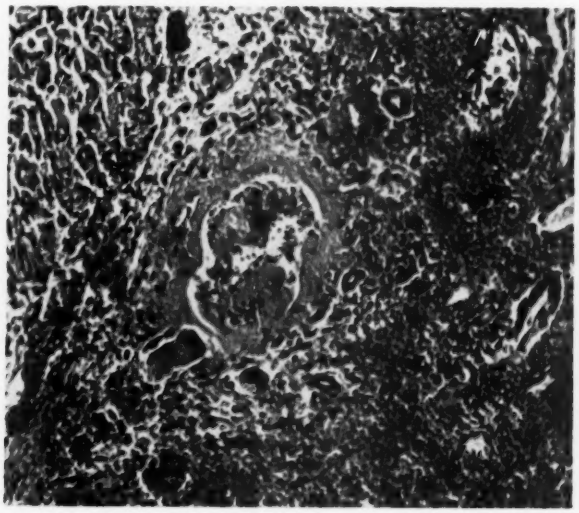


Fig. 6.—Small vessel with irregularly thickened smudged necrotic wall and surrounding interstitial fresh hemorrhage in the left kidney. Hematoxylin and eosin; × 155.

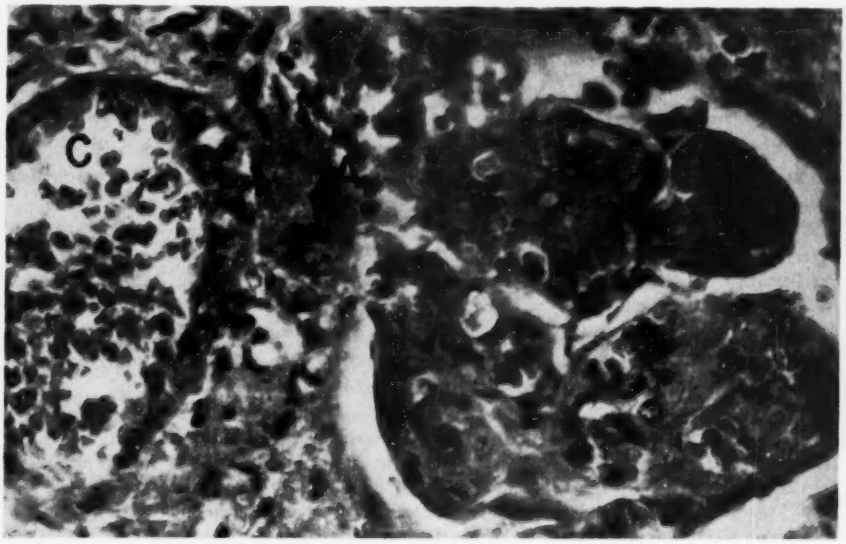


Fig. 7.—*A*, afferent arteriole in the left kidney, with completely disintegrated necrotic wall; *B*, acute focal necrosis of glomerulus; *C*, fresh hemorrhage within adjacent tubule. Hematoxylin and eosin; × 550.

COMMENT

Goldblatt and his associates [1] demonstrated experimentally in dogs that sustained hypertension may result from partial constriction of both renal arteries or from constriction of one renal artery followed by the removal of the opposite kidney. Malignant hypertension with renal insufficiency and a short course followed severe constriction of both renal arteries, or constriction of one and the occlusion of the ureter of the contralateral kidney. Microscopically, arteriolonecrosis and hemorrhages were found in the kidney with the patent renal artery and in other organs, but the kidney with the constricted renal artery was notable for the absence of acute necrotizing vascular changes. Goldblatt concluded that only those arterioles become necrotic that are subjected both to high bursting tension and to the effects of chemical substances in the blood which result from renal damage. Wilson and Byrom [2] demonstrated persistent hypertension in rats with partial constriction of one renal artery. The animals manifested weakness, wasting, and coma, but no renal insufficiency. Resection of the clamped kidney resulted in improvement. Microscopically, arteriolonecrosis in organs including the unclamped kidney was found. The latter resembled lesions of malignant hypertension in man. In the kidney with the renal artery constriction tubular atrophy and partial infarction were sometimes noted but arteriolonecrosis was not found. These workers felt that the arteriolar necrosis was due to vascular strain imposed by a rapidly developing hypertension and that renal failure was not an etiologic factor.

In the years following these experiments, cases of human hypertension related to obstructive lesions of the main renal arteries have been reported. These occlusions have been due to arteriosclerotic narrowing,[4] extrinsic compression,[5] and thrombotic and embolic involvement of renal arteries.[6] Yuile,[3] in an extensive review of the literature through 1944, favors the view that atheromatous plaques in renal arteries occur in a high percentage of people with essential hypertension but these lesions are secondary or incidental to the hypertension rather than causative, since the lesions of large vessels are commonly associated with intrarenal arteriolar sclerosis.

4. (*a*) Howard, T. L.; Forbes, R. P., and Lipscomb, W. R.: Aneurysm of Left Renal Artery in Child 5 Years Old with Persistent Hypertension, J. Urol. **44**:808-815 (Dec.) 1940. (*b*) Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353-375 (Nov.) 1939. (*c*) Yuile.[3]

5. Leadbetter, W. F., and Burkland, C. E.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611-626 (May) 1938. Howard, Forbes, and Lipscomb. [4a]

6. (*a*) Goodman, H. L.: Malignant Hypertension with Unilateral Renal-Artery Occlusion, New England J. Med. **246**:8-12 (Jan. 3) 1952. (*b*) Saphir, O., and Ballinger, J.: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis, Arch. Int. Med. **66**:541-560 (Sept.) 1940. (*c*) Fishberg, A. M.: Hypertension Due to Renal Embolism, J. A. M. A. **119**:551-553. (June 13) 1942. (*d*) Prinzmetal, M.; Hiatt, N., and Tragerman, L.: Hypertension in a Patient with Bilateral Renal Infarction: Clinical Confirmation of Experiments in Animals, ibid. **118**:44-46 (Jan. 3) 1942. (*e*) Blahd, W. H.; Marcus, R., and Wasserman, D. M.: A Case of Malignant Hypertension Secondary to Renal Ischemia, Ann. Int. Med. **37**:179-185 (July) 1952. (*f*) Laforet, E. G.: Malignant Hypertension Associated with Unilateral Renal Artery Occlusion: 3 Cases, ibid. **38**:667-688 (April) 1953. (*g*) Yuile. [3]

Cases of malignant hypertension resulting from renal artery occlusions have been reported.[7] Malignant hypertension as described by Allen [8] and Fishberg [9] is a clinical entity with fulminating hypertension, papilledema, and renal insufficiency. Malignant nephrosclerosis, the anatomical renal changes accompanying malignant hypertension, may not occur because of death due to cerebral hemorrhage or congestive heart failure.[10] Prinzmetal, Hiatt, and Tragerman [6d] reported a case in which a patient with a short course of malignant hypertension died in uremia. At postmortem examination, both renal arteries were found to be occluded by thrombus and both kidneys were extensively infarcted. Vascular lesions associated with malignant hypertension were not described. Perfusate of one kidney contained a pressor substance similar to that found in perfusates of ischemic kidneys of animals.

Saphir and Ballinger [6b] presented a case of a 45-year-old man in whom hypertension was noted five years before terminal heart failure and uremia. At autopsy the left renal artery was almost completely occluded by old and recent thrombus. The left kidney revealed no abnormality other than a small area of infarction, and the right showed a microscopic picture of malignant nephrosclerosis. A similar case of malignant hypertension terminating in uremia following complete occlusion of a renal artery was described by Aronson and Sampson.[11] Arteriolar necrosis was found in the unoccluded kidney only. Blahd and his associates [6e] reported a case in which fulminating hypertension and renal failure occurred after occlusion of a renal artery. There was no arteriolosclerosis or necrosis in the ischemic kidney. Glomerulitis and arteriolar sclerosis were found in the nonischemic kidney, and similar vascular changes were noted in the gastrointestinal tract, adrenal glands, lungs, and pancreas.

Goodman [6a] reported a case of malignant hypertension without uremia resulting from old thrombotic occlusion of the right renal artery. There was no arteriolar sclerosis in the ischemic kidney. The vascular change of the nonischemic kidney consisted of hyperplastic arteriolar sclerosis. There was no evidence of necrotizing arteriolitis or glomerulitis in this kidney. Of three cases of malignant hypertension with unilateral renal artery occlusion with no evidence of renal failure reported by Laforet [6f] in only one was there no arteriolar sclerosis in the ischemic kidney. In all three cases necrotizing arteriolar lesions in the nonischemic kidney were seen. Fisher and Corcoran [7] describe a case of malignant hypertension in a 14-year-old boy, resulting from stenosis of renal artery ostia due to coarctation of the aorta. There were clinically fulminating hypertension and papilledema, but renal function was normal. Except for several adventitial vessels in the aorta with "fibrinoid change," all other small vessels were unremarkable. Malignant nephrosclerosis was absent.

7. Fisher, E. R., and Corcoran, A. C.: Congenital Coarctation of Abdominal Aorta with Resulting Renal Hypertension, A. M. A. Arch. Int. Med. **89**:943-950 (June) 1952. Footnote 6.

8. Allen, A. C.: The Kidney, Medical and Surgical Diseases, New York, Grune & Stratton, Inc., 1951, pp. 396-416.

9. Fishberg, A. M.: Hypertension and Nephritis, Ed. 4, Philadelphia, Lea & Febiger, 1939, pp. 674-682.

10. Kimmelstiel, P., and Wilson, C.: Benign and Malignant Hypertension and Nephrosclerosis: Clinical and Pathological Study, Am. J. Path. **12**:45-82 (Jan.) 1936. Fishberg.[9]

11. Aronson, S. M., and Sampson, M. C.: Unilateral Renal Cortical Necrosis and Unilateral Benign and Malignant Nephrosclerosis Associated with Contralateral Renal Artery Occlusion: Report of Case, A. M. A. Arch. Path. **51**:30-37 (Jan.) 1951.

In this particular case our interpretations of the findings were that the mesaortitis was the nidus for the formation of the aortic plaque. This plaque was many months old and antedated the onset of the hypertension. The plaque extended into the left renal ostium, obstructing about one-third of the lumen (Figs 1*B* and 2*B*). An extension of the aortic plaque into the right renal artery resulted in almost complete occlusion (Fig. 4*A*) and ischemic atrophy of the right kidney. The small lumina in the old thrombus in the right renal artery were completely occluded by recent unorganized thrombi (Fig. 4*B*), which were several weeks old. The age of these thrombi, which may have initiated the hypertension, was temporally related to the duration of the course of malignant hypertension. Necrosis of arterioles, which probably resulted from the sudden high vascular tension,[12] was found in the left kidney, brain, adventitia of the aorta, and adrenal glands. Fresh hemorrhages occurred in the left (nonischemic) kidney, muscle, lungs, adrenal glands, ovaries, and brain. The massive intracerebral hemorrhages resulted in death.

It is interesting to note that the right kidney, which had a completely occluded renal artery and thus was protected from the sudden increase in blood pressure, showed recent infarcts but no arteriolonecrosis or hemorrhages.

In view of the available data concerning renal function, i. e., an apparently normal, but not measured, urinary output and a slightly elevated blood urea nitrogen 30 hours before death, it appears that renal insufficiency may not have been a factor in the production of necrotizing arteriolitis. Fishberg[9] reported that in malignant hypertension in man necrosis of renal arterioles could occur before significant renal insufficiency developed.

This case was similar anatomically to those reported by Saphir and Ballinger,[6b] Aronson and Sampson,[11] and Blahd and his associates,[6e] in which arteriolonecrosis was present in the kidneys with unoccluded renal arteries; it differed clinically from these cases, however, in that there was no uremia. It resembled clinically the case reported by Fisher and Corcoran,[7] in which death followed cerebral hemorrhage before renal failure developed, and it differed anatomically from the latter case in that there was widespread arteriolonecrosis.

The series of events in this patient resulting in malignant hypertension of renal origin appears to resemble that produced experimentally.[13]

The problem of the presence of syphilis in this patient was perplexing. There were no clinical signs of the disease. It is possible that the numerous first trimester abortions were due to syphilis. This, however, was unlikely, because syphilis seldom or never causes early abortions.[14] Examination of products of conception from these eight abortions revealed no evidence of syphilis. The slides from material of one of these abortions, reviewed in this laboratory, showed no evidence of syphilitic infection. Extensive serological studies were inconclusive. Several serologists agreed that the patient's serum was producing a false positive reaction for syphilis. The postmortem examination disclosed no evidence of the disease in the central nervous system and vascular tree, except possibly the mesaortitis.

12. Wilson, C., and Byrom, F. B.: The Vicious Circle in Chronic Bright Disease: Experimental Evidence from Hypertensive Rat, Quart. J. Med. **10**:65-93 (April) 1941. Goldblatt.[1] Wilson and Byrom.[2]

13. Goldblatt.[1] Wilson and Byrom.[2]

14. Beck, A. C.: Obstetrical Practice, Ed. 4, Baltimore, Williams & Wilkins Company, 1947, pp. 487.

This mesaortitis is unusual for one due to syphilis. Its location was below the diaphragm and it was focal rather than diffuse. The intensity of the inflammation was marked at the level of the origin of the renal arteries, diminishing rapidly a few centimeters above and below this point. Macroscopic examination of the aorta showed that the intima presented none of the diffuse irregular thickening and deep crevices associated with syphilitic infection. The microscopic study revealed disruption of elastic fibers in the media at intervals, which were not converted into scar tissue with vascularization. The cells invading the media were focally disseminated and did not form long streaks or collars around the vasa vasorum, as would accord with those found in syphilis. Sections prepared with special stains to demonstrate spirochetes and bacteria were negative. The points of similarity with syphilitic aortitis were predominance of the lymphocyte as the inflammatory cell, thickening of the adventitia, and increase in number of vasa vasorum. It was concluded that the mesaortitis was not due to syphilis and that it bore some similarities to two cases of chronic diffuse mesaortitis of unknown cause described by Sproul and Hawthorne.[15]

This case is unusual in that the patient was a young woman with a history of normotension well documented and in whom the course of hypertension was definitely known to be not more than two months.

The abdominal pain noted eight weeks before her death was related in time to the right renal infarcts. The coma and meningismus were related to the cerebral hemorrhages, of a few days' duration. Renal insufficiency did not occur, possibly because of the fatal cerebral hemorrhages.

Unexplained were the cause of the numerous abortions, the etiology of the thrombophlebitis, mesaortitis, the sclerosed vessels in the choroid and in the brain, and the foci of old malacia in the cerebral cortex.

SUMMARY

A case of malignant hypertension of short duration in a young woman with a documented history of normotension is reported with autopsy findings.

A thrombotic aortic plaque with extensions into the main renal arteries, antedating the onset of hypertension, was superimposed upon a mesaortitis of unknown cause.

The sudden complete occlusion of a renal artery was related in time to the onset of malignant hypertension. The duration of the malignant hypertension was correlated with the age of the renal arterial occlusion.

Arteriolonecrosis of the nonischemic kidney, brain, adrenal glands, and aorta was found. The vessels of the kidney with a completely occluded renal artery were unremarkable.

15. Sproul, E. E., and Hawthorne, J. J.: Chronic Diffuse Mesaortitis: Report of 2 Cases of Unusual Type, Am. J. Path. **13**:311-323 (March) 1937.

Books

Clinical Endocrinology. By Lewis M. Hurxthal, M.D., and Natalija Musulin, M.D. Price, $24.00. Pp. 1,599, with 482 figures, 146 charts, and 121 tables. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, 1953.

This two-volume book probably will become a standard reference for clinical endocrinology. The authors, combining years of clinical experience with an extensive study of the literature, have produced a comprehensive book that should prove welcome to physicians interested in this rapidly expanding field.

The two volumes contain a total of 25 chapters. Each endocrine gland is dealt with in a separate chapter that is divided into preclinical and clinical parts. The preclinical part includes sections on the anatomy, embryology, anomalies, histology, functions, chemistry, bioassay, and pathology of the particular gland under consideration, together with other basic information. Included in the preclinical part is a helpful section listing specific points and facts to be looked for in the history, physical examination, and laboratory study of the patient. The clinical part of each chapter is concerned with the diagnosis and treatment of the various syndromes caused by dysfunction of the gland.

In addition to the chapters devoted to specific endocrine glands, there are instructive chapters on topics such as growth and development, hermaphrodism, sterility, dwarfism, growth of hair in relation to the endocrine glands, obesity, endocrine aspects of hypertension, adaptation syndrome, endocrine role of the liver, mammary glands, gastrointestinal hormones, antihormones, and the bioassay and uses of pituitary and chorionic hormones and the steroid compounds.

The text is well illustrated, with 482 figures, 146 charts, and 121 tables. Reports of 39 cases are presented as classic and illustrative examples of various endocrinologic syndromes. The bibliography is extensive yet includes only carefully selected references.

The book is well organized for ready reference. It is written in the form of an outline, which enhances its usefulness as a reference book. On the other hand, this form makes it difficult to read the text at times and does not give the authors a satisfactory medium for discussion of the many controversial aspects of clinical endocrinology.

This work is recommended as a reference book on clinical endocrinology. Persons who dislike a text written in the form of an outline may wish to examine the book before acquiring it.

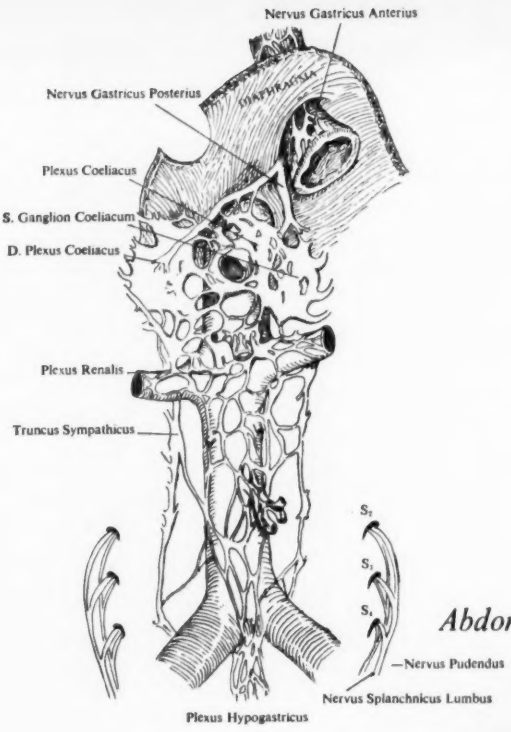
Physiological and Therapeutic Effects of Corticotropin (ACTH) and Cortisone. By Dwight Joyce Ingle and B. L. Baker. Price, $5.50. Pp. 172, with 17 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1953.

"Physiological and Therapeutic Effects of Corticotropin (ACTH) and Cortisone" offers the reader a short fairly concise review of the subject outlined in the title. The book's main contribution is contained in the first half, in which the physiological aspects of the steroids are discussed with reference to the initial research studies involved. The steroids are compared as to their effect on various functions of body physiology, such as "survival and vigor," "circulation," "pain," "organic metabolism," "growth," and "electrolyte and water metabolism."

The facts gained through the numerous research studies in the field do not, however, reduce themselves into a compact and simple theory. The results of these studies at times appear to be inconsistent, even contradictory. It is not an easy book to read, nor are the facts included easily absorbed. But, besides the value of a thorough review of the basic physiology, one needs a reminder of the widespread effect of the drugs and of the immensity of the undiscovered.

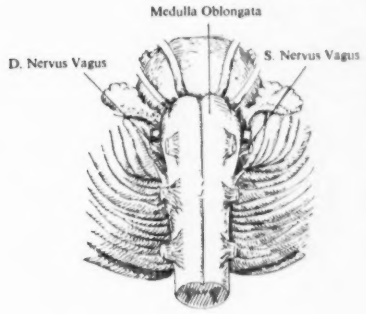
The authors are biologists, not physicians, and therefore the section on therapy, although occupying approximately one half of the 172-page book, is actually only a summarized review of the literature.

The bibliography is of considerable length, consisting of 324 references on the subject.



Abdominal autonomic plexus (sympathetic)

Central origin of the vagus nerves (parasympathetic)



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1. Zupko, A. G.: Pharmacology and the General Practitioner, GP 7:55 (March) 1953.

2. McHardy, G. G., and Others: Clinical Evaluation of Methantheline (Banthine) Bromide in Gastroenterology, J.A.M.A. *147*:1620 (Dec. 22) 1951.

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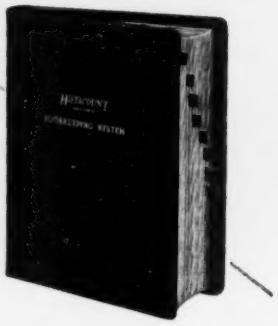

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BIBLIOGRAPHY: *1. Humphreys, P., et al.: Angiology* 3:1 *(Feb.) 1952. 2. Plotz, M.: New York State J. Med.* 52:2012 *(Aug. 15) 1952. 3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.*

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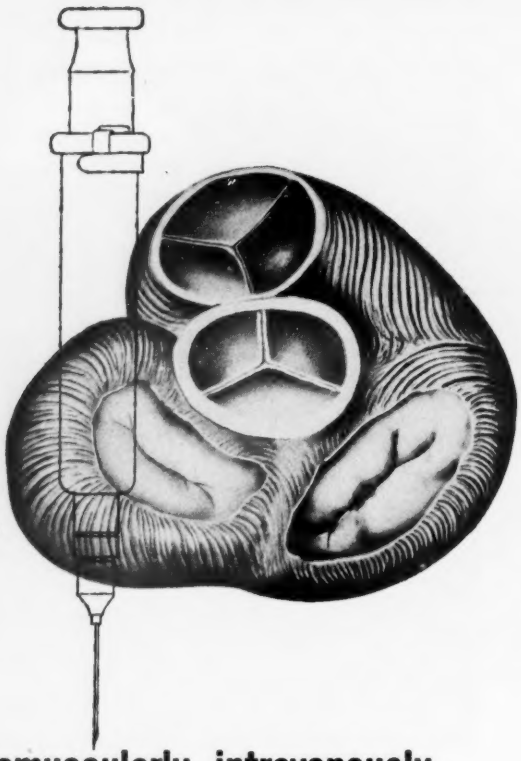

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*Marsh, R.; Greiner, T.; Gold, H.; Mathes, S.; Palumbo, F.; Warshaw, L., and Weaver, J.: New England J. Med. *247*:593 (Oct. 16) 1952.

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